GENERAL LIBRARY
OCT 14 1918
UNIV. OF MICH.

BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice
Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917. Authorized on July 3, 1918.

Vol. XXIX—No. 332] BALTIMORE, OCTOBER, 1918 [Price, 50 Cents

CONTENTS

PAGE

Myrtol Poisoning; With Comments upon the Toxicity of Eucalyptus Oil and Myrtol in Human Beings and in Animals.
By Lewellys F. Barker, M. D., and Leonard G. Rowntree, M. D. 215

Dakin's Solution and Dakin's Oil in the Normal Peritoneal Cavity of the Dog.
By Ernest G. Grey, M. D. 221

Multiple Primary Malignant Tumors. With Report of a Case of Carcinoma and Sarcoma in the Same Individual. (Illustrated.)
By Ralph H. Major 223

PAGE

Idiopathic Bacillus Aerogenes Capsulatus Infection. (Illustrated.)
By Horace Greeley, M. D. 231

Abstract of Paper. 235
Observations upon the Calcium Content of the Blood in Infantile Tetany and upon the Effect of Treatment with Calcium [John Howland and W. McKim Marriott].

Books Received 239

MYRTOL POISONING; WITH COMMENTS UPON THE TOXICITY OF EUCALYPTUS OIL AND MYRTOL IN HUMAN BEINGS AND IN ANIMALS

By Lewellys F. Barker, M. D., and Leonard G. Rowntree, M. D.

(From the Medical Clinic of The Johns Hopkins Hospital and the Pharmacological Laboratory of The Johns Hopkins University)

On account of the toxic symptoms that sometimes follow the administration of oil of eucalyptus and allied substances, it would seem worth while to report the following case of alleged poisoning by myrtol:

Clinical History

The patient, a gentleman 42 years of age, consulted one of us on January 10, 1911, complaining of cough with a large amount of offensive sputum. The family history is negative for tuberculosis. The patient had pneumonia at the age of 21, since when he has had more or less cough and sputum. During the past five years the cough has been worse and a considerable amount of sputum has been coughed up each morning. Five years ago, after an acute cold with sore throat, he suffered from hæmoptysis, coughing up half a teacupful of blood. Repeated examinations for tubercle bacilli were made, but none was found. There was no fever during the attack. In September, 1911, before consulting us, he had had an acute bronchitis accompanied by slight hæmoptysis. This was followed by a bronchopneumonia involving the upper lobe of the right lung, the illness lasting over one month. Many examinations for tubercle bacilli were made during this period, always with negative results. An autogenous vaccine was prepared by his local physician against some microorganism grown from the sputum and five doses were administered.

Note made on January 10, 1911 (Dr. Barker).—The patient now feels very well, though he still coughs up a considerable amount of sputum, especially in the morning, and this sputum is very offensive at times. The total amount raised now is about four ounces in the 24 hours. There is no pain and no dyspnœa. The voice is occasionally hoarse. No night sweats. No marked digestive disturbance. Weight 227 pounds. Height 6 feet 2 inches. The weight was 245 pounds before the attack of bronchopneumonia.

Physical Examination.—Slight protrusio bulborum; positive von Graefe's sign. Defective teeth. No struma. No glandular enlargements.

Right upper chest flatter than left in front. Right mammilla on lower level than left. Expansion greater in left chest; right lung lags behind. Breath sounds slightly prolonged at right apex, and the percussion note is a little higher pitched there than on the left. No râles audible in upper lobes. Fremitus somewhat more marked over the right suprascapular region than over the left. Breath sounds distant at the right base. A distinct creaking sound is audible at the right base, and some distant moist râles can be heard there. Breath sounds and voice sounds are distant over right lower lobe behind.

Heart negative. Abdomen negative. Reflexes normal.

X-ray Examination (Dr. F. H. Baetjer).—Stereoscopic and radiographic examination of the chest shows increase of fibrous tissue around the bronchi and the bronchial ramifications in both lungs. Some enlarged glands at the hilum of the left lung. Left lung substance clear throughout.

A peculiar shadow is seen at the base of the right lung, obliterating the diaphragm and the base of the right lower lobe. This shadow is probably due to a thickened pleura and to some fibroid change in the lung itself. In the upper part of the right lower lobe the bronchial tree can be distinctly made out. There is a suggestion of a bronchiectatic cavity in the right lower lobe, but there is so much fibrous peribronchial change that no definite statement regarding it dare be made.

Diagnosis.—Bronchiectasis; bronchitis chronica putrida; peribronchitis fibrosa; pleuritis chronica dextra.

Treatment.—In addition to general measures, three minims of myrtol in capsules thrice daily were prescribed on account of the fœtid bronchitis. The patient had been taking some oil of eucalyptus and oil of sandalwood before. These he continued along with the myrtol.

Further Course.—January 16. The patient reports that the myrtol is already lessening the putrid odor of the sputum.

February 13. The patient writes from the Pacific Coast that he has suffered strange and severe symptoms since taking the myrtol prescribed. After having taken two capsules three times a day for eight days "the face became discolored and large 'puffs' came under each eye. The forehead looked as if it were going to break out with eczema. The left eye became nearly closed and the right partially closed from the swelling."

Fearing an attack of erysipelas he called a local physician, who, with the nurse, agreed that the symptoms must be due to the poisonous effects of the myrtol. The drug was stopped at once, but the swelling lasted for many days. The patient states that the cough increased markedly and that the heart's action became more rapid, and that he was greatly depressed. He had been told to increase the dose of myrtol gradually until 12 capsules per day were taken, but the myrtol was stopped when only six capsules per day were ingested. He states that the discoloration of the skin and eruption covered the entire chest also.

February 28. The patient writes that he and the nurse feel entirely convinced that the whole trouble was caused by the myrtol. He sends the bottle containing the unused portion of the drug that experiments may be undertaken with it. It was purchased from a druggist in Baltimore, who stated that it had come direct from Merck's in New York.

In one of the patient's later letters, he states that he is not sure that the offensive odor of the breath was really decreased by the myrtol. He also states that while on the train going toward the Pacific Coast, during the last two days of the trip, he was in serious doubt as to whether he would reach his destination alive.

Here we have evidently to deal with an instance of myrtol intoxication, probably exaggerated by the oil of eucalyptus which was taken at the same time. The striking phenomena observed in this patient, never before observed by us notwithstanding a considerable earlier experience in myrtol administration, led us to try some experiments on animals and to review the literature of the subject.

Sources of Myrtol and Eucalyptol

Myrtol, obtained by distillation from the leaves of *Myrtus communis,* is a mixture of a dextrorotary terpene (known as cineol), pinene, $C_{16}H_{18}O$ and dipentene. The myrtol, on distillation, comes over between 160° and 180° C.

Oil of eucalyptus is a volatile oil distilled from the fresh leaves of eucalyptus, rectified by steam distillation; it yields, when assayed, 50 per cent of eucalyptol.

Eucalyptol ($C_{10}H_{18}O$) is the chief constituent of the eucalyptus oil obtained from *Eucalyptus globulus* and some other species. It is an organic oxide (optically inactive) isomeric with cajeputol (levorotary), and with cineol (dextrorotary). In the distillation of eucalyptus leaves the portion that comes over between 170° and 178° C. is set aside as crude eucalyptol. When redistilled from potassium hydroxide, pure eucalyptol is obtained.

The large natural order, *Myrtaceæ,* includes many genera. Among them besides *Eucalyptus* and *Myrtus* may be mentioned *Pimenta* (allspice) and *Eugenia* (cloves). The oils from these several myrtaceous species are utilized to a considerable extent as remedial agents.

Eucalyptus oil, eucalyptol, and myrtol find their chief value in therapeutics, at present, in the treatment of catarrhal conditions of the respiratory mucous membrane; they are administered either internally (on sugar, or in capsule) or with steam in the vapor from an inhaling apparatus. They are also occasionally employed (1) in chronic inflammation of the genitourinary mucous membranes; (2) locally as an antiseptic dressing to ulcers; and (3) also as counterirritants in neuralgia and rheumatism. Eucalyptus oil and eucalyptol are usually administered in 5-10 minim doses and myrtol in 5-15 minim doses, in capsule, four to eight times a day.

Formerly, eucalyptus oil was utilized much more extensively than at present. It was thought to possess considerable value as an antiperiodic and hence was widely used in the treatment of malaria. It was administered in these cases in large doses (usually from ½ to 1 drachm) two or three hours before the expected paroxysm. The subcutaneous administration was frequently resorted to, the oil being diluted in olive oil (1 in 4 or 1 in 10). It has also been used locally in the treatment of various skin diseases, *e. g.,* in eczema, prurigo, psoriasis, impetigo and condylomata. Recently, since Dakin's introduction of chloramin therapy, oil of eucalyptus has begun to be extensively used, and it will be interesting to observe whether many instances of intoxication are met with.

Animal Experiments (Dr. Rowntree)

Some experiments were made upon dogs and cats with myrtol and with eucalyptus oil in order to determine their toxicity. The data relating to the myrtol experiments are first presented. Since the bottle of myrtol used by the patient was only partially emptied, the remainder was available for study. It is here designated as Preparation I. Another sample of myrtol (Preparation II) was obtained from a local druggist. The drug was administered to the animals through a stomach tube.

TABLE I.—EFFECT OF MYRTOL ON DOGS

Dog	Weight in kg.	Date	Amount administered	Condition of animal
I	9.9	3-11-11	1 c. c. of Prep. I.	No abnormality noted.
		3-13-11	5 c. c. of Prep. I.	Dog did not vomit this. He took his food and drink normally. He remained normal.
II	9.3	3-11-11	0.8 c. c. of Prep. I.	This dog remained perfectly normal throughout the period of observation from March 11 to March 25.
		3-12-11	2 c. c. of Prep. I.	
		3-14-11	2 c. c. of Prep. I.	
		3-15-11	2 c. c. of Prep. II.	
III	6.2	3-13-11	2 c. c. of Prep. I.	Vomited five minutes after first administration. Remained free from vomiting after other doses until the 22d. On this date the dog vomited 10 minutes after the administration. The vomited oil was intimately mixed with meat. The dog ate this again and was entirely normal after it. No sign of a skin lesion developed.
		3-14-11	0.5 c. c. of Prep. I.	
		3-16-11	2 c. c. of Prep. II.	
		3-17-11	2 c. c. of Prep. II.	
		3-18-11	2 c. c. of Prep. II.	
		3-19-11	2 c. c. of Prep. II.	
		3-20-11	2 c. c. of Prep. II.	
		3-21-11	2 c. c. of Prep. II.	
		3-22-11	2 c. c. of Prep. II.	
IV	5	3-15-11	0.5 c. c. of Prep. I.	This dog remained absolutely normal until the 21st. On this date coryza and diarrhœa were noted. Dog developed a typical distemper and so was discarded. No skin rash.
		3-16-11	0.5 c. c. of Prep. I.	
		3-17-11	0.5 c. c. of Prep. I.	
		3-18-11	0.5 c. c. of Prep. I.	
		3-20-11	0.5 c. c. of Prep. I.	
		3-21-11	0.5 c. c. of Prep. I.	
V	5	4- 5-11	5 c. c. of Prep. I.	Dog did not vomit. No ill effect noted.
VI	4	4- 2-11	2 c. c. of Prep. II every day for a period of two weeks.	Outside of a slight loss of appetite no abnormal condition was noted. No rash appeared.

Careful examination of the skin was repeatedly made on all of these animals, but at no time was there noted any skin rash ascribable to the drug.

In the following experiments, however, severe toxic phenomena followed subcutaneous and intraperitoneal administration.

Exp. VII.—Dog. 7.3 kg. Very playful. Pulse 150, respirations 36, temperature 38°.

12.24 10 c. c. eucalyptus oil in 30 c. c. olive oil subcutaneously.

12.30 Has lost playfulness, will not eat meat. Marked odor to breath. Sits in the corner, saliva dripping from mouth. Pulse and respiration unchanged at 12.40. Dizzy, does not respond well to prodding, apparently somewhat anæsthetic.

1.20 Pulse 180, respiration 36; very dizzy.

3.20 Staggering, lies in a corner. Fæces and urine passed and the dog lies in them. Pulse 180. Pupils normal.

5 p. m. Respiration 30, temperature 39°. Marked collapse. Pulse cannot be felt, but a rate of 200 is determined by auscultating heart. Dog has been lying in her urine and fæces; can scarcely walk. Pupils slightly larger than normal, and contract to light.

7 p. m. Condition unchanged.

The following morning the animal had the odor of eucalyptus on its breath, but was running about, apparently in normal condition. Pulse 104, respiration 24, temperature 37.5° C.

Two days later: odor still present in breath. Fæces and urine free from odor. Dog normal.

Exp. VIII.—A cat (1.8 kg.) was given subcutaneously 5 c. c. of Preparation II in 15 c. c. olive oil on December 8. After 10 minutes it seemed somewhat restless, but otherwise normal. The pulse, respirations and temperature remained unchanged during a period of observation of five hours. On December 9 the animal was somewhat ataxic, presenting a staggering gait. It refused to eat or drink. The breath smelled strongly of eucalyptus oil. The pupils remained normal. The urine was dark in color, showed a trace of albumin, but no sugar. Casts and blood were absent. Respiration, pulse and temperature normal. On the following day the animal was much better, walked without staggering, but still refused water and food. Urine showed a slight trace of albumin. On the 11th it drank milk and took its food and was apparently normal again.

Exp. IX.—Eucalyptus oil in toxic doses was also administered to two cats. Cat I (2 kg.) was given 10 c. c. of eucalyptus oil in 30 c. c. of olive oil intraperitoneally at 12.30. At 12.38 it appeared unsteady on its feet and swayed from side to side when attempting to walk. Stringy mucus was secreted from the mouth. At 12.40 it huddled up in a corner and refused to move. At 12.47 all power of motion was lost. The animal apparently was anæsthetized inasmuch as no response to prodding with a needle could be elicited. A slight clonic convulsion was seen at 12.50. This became more marked, following any sudden sharp noise, *e. g.*, clapping of hands. Respiration normal, pulse 112. Temperature 37° (normal, taken before giving oil, 38.5° C.). The pupils remained normal. Animal comatose. Death at 2.30 p. m.

Exp. X.—Cat II. (1.8 kg.) 10 c. c. eucalyptus oil at 1 p. m., subcutaneously. The animal appeared dizzy at 3 p. m., staggering on attempting to walk. At 8 p. m. this was more marked. The following morning the animal was found in a semi-comatose condition. Convulsions occurred at intervals. Temperature was low, 29° C., by rectum. Pulse 92, respirations 14. Urine high-colored and scanty, containing blood and albumin, but no casts. The odor of eucalyptus on breath was very marked. Chlorobutanol gm. 1.0 was administered, followed by death in the course of an hour.

Bruning has determined the toxicity of eucalyptus oil for animals and finds that, in the frog, 0.5 c. c. per kilo caused only temporary paralysis, in toads 1 c. c. per kilo did not kill constantly, in fish a solution of 1:10000 was tolerated, in chickens 0.3 c. c., in rabbits 1 to 5 c. c. and in guinea-pigs 1 c. c. per kilo was not fatal. He states that small doses are dangerous to children and advises against its employment in the treatment of ascaris lumbricoides.

REVIEW OF LITERATURE

In looking over the literature nothing seems to be recorded regarding the toxicity of myrtol, but with eucalyptus oil we find that cases of poisoning have not been uncommon. The cases reported may be divided into two classes:

I. Cases in which overdoses have been taken accidentally or through ignorance, following which grave symptoms of intoxication have been present; some of the patients recovered more or less gradually; some died.

II. Cases in which the patient has responded in an unexpected and unaccountable way to minute or therapeutic amounts of eucalyptus preparations.

CASE I.—Beginning with cases of the first class: Wood (1879) reported a case of poisoning with belladonna and eucalyptus. A man, aged 48, received ½ ounce of belladonna root together with

3 drachms of eucalyptus oil. Six hours later, when first seen, he was unconscious, with widely dilated pupils which did not respond to light. Pulse 110, full and strong; respirations rapid. Spasmodic twitchings of the extremities. After the stomach had been emptied with a tube, the patient was stimulated electrically and on partial revival was made to move about and to walk between assistants for a period of five hours. At the end of this time he was still in a dazed condition and was hyperæsthetic over the whole skin. Strong coffee and milk were given and also 4 minims of tincture of opium. On the following day, dryness of the throat, thirst, and pruritus were complained of. At the same time, the skin of the patient showed a red blush. which lasted for two days. At the end of two weeks, the patient left the hospital, apparently in a normal condition.

Case II.—Owen (1885) made a report of a child, 17 months old, who swallowed the drippings from a bottle of fluid extract of eucalyptus. Within a half hour it became drowsy and lost all power in the limbs. The child was pale, its head and extremities were cold, the pupils were contracted, the conjunctivæ were insensitive, the pulse was imperceptible, and the respirations were short and spasmodic. The child could be aroused. Following a soap and lime water emetic, it vomited three times. Whiskey, warm milk and lime water were administered; the child was put to bed and artificial heat was applied. Two and a half hours later, the pulse was feeble and small, but the patient was less drowsy. Castor oil was then administered. The temperature rose, and 36 hours after the ingestion of the eucalyptus had reached 102° F.; the respirations were 60 to the minute. A slight cough and rhonchi were noted. Five days later the child had fully recovered.

Case III.—Sheaf (1888) reported that a man 25 years old developed vertigo one and one-quarter hours after taking 5 drachms of eucalyptus oil. The patient talked loudly, and exhibited involuntary twitchings of the fingers. He did not vomit. He was conscious two hours later, but the pulse was weak and rapid. Emetics were used and caffeine and sodium salicylate administered. The patient recovered completely.

Case IV.—Wood (1888) cited a case of Gimbert's: An old man took 80 minims of eucalyptus oil. The power of motion almost disappeared and the patient affirmed that he had lost, for the time being, all sense of the presence of his limbs, so that he was unconscious of them when he shut his eyes. His intellect was perfectly clear throughout.

Case V.—Wood also stated that Binz had described a similar condition after 75 minims had been taken.

Case VI.—Neal (1893) reported that a healthy boy, 10 years old, took some eucalyptus (½ drachm of blue gum) for prophylactic reasons just before going to bed. In a few moments he was gasping for breath. He vomited and felt much better. Dyspnœa became marked, however, one hour later, but no convulsions or diarrhœa were noted. The lips and gums were colorless, the chest and neck rigid, and the pulse feeble and rapid. He complained of pain in the right chest, which was relieved by poultices. The intellect remained clear until one hour before death.

At the autopsy, the stomach was found to be much distended with gas, the gastric mucosa being white, thickened, and puckered. There was a quart of fluid in the pleural cavities; the lungs were collapsed, firm and bloodless. The right heart contained frothy liquid blood.

Cases VII and VIII.—Neal quoted Martindale as having given 80 minims of eucalyptus oil in two and one-half hours. He also mentioned a case in which Croker of Geeling had asserted that a man's death was accelerated by a dose of 1 ounce of eucalyptus.

Case IX.—Lewin (1897) stated that a boy, 16 years old, after 15 c. c. of the oil, vomited and went into a state of collapse. Dyspnœa and air hunger were noted. The boy died within 15 hours, and at autopsy blood was found in the pleural cavities.

Case X.—Manquat (1898) speaks of Siegen's case in which the ingestion of 3.5 c. c. of the oil of eucalyptus was followed by headache, drunkenness, stupor, somnolence, weakened reflexes, enfeebled respiration, lowered blood-pressure, decreased temperature, and eventually by paralysis of respiration.

Cases XI and XII.—Kunkel (1899) describes two cases:

(1) A child, three years old, took a small spoonful of eucalyptus oil. He estimated that the amount was about 8 c. c. Vomiting was followed by speedy recovery.

(2) A boy, 10 years old, took 15 c. c. of eucalyptus oil and died in collapse 15 hours later.

Case XIII.—Thomas (1899) reports the poisoning of a baby boy, 4 weeks old, with 1 drachm of eucalyptus oil. When seen the patient was comatose; harsh breathing and the odor of the drug on the breath were noted. Ipecac was given and repeated in half an hour. Stimulants were of no avail. Death occurred four hours after the administration of the oil. There was no emesis.

Case XIV.—Wood (1900) reported that a child three years old grew violently sick within two hours after taking 2 or 3 drachms of the oil. Drowsiness, stupor and collapse developed, along with pin-point pupils. The symptoms lasted 10 hours, but the patient recovered. Except for the absence of stertorous breathing, the condition was described as identical with that encountered in opium poisoning.

Case XV.—Taylor (1905) stated that a man, 25 years old, took 1 drachm of eucalyptus, and within a few minutes had pain along the œsophagus and in the gastric region. After a time, he became dazed and suffered from a feeling of impending suffocation. He was at first very restless, but later became semicomatose. The pupils were slightly contracted.

Emetics and stimulants were successfully employed, and the following morning the patient was apparently well.

Cases XVI and XVII.—Benham (1905) reported two cases:

(1) A man, 41 years of age, became comatose after swallowing 1 drachm of the oil. Emetics were successful; the man was entirely well in a few hours.

(2) A young man showed similar symptoms after 1 drachm of the oil. Emetics were employed and the patient recovered.

Case XVIII.—Smith (1906) investigated a case of poisoning by half a wine-glassful of eucalyptus oil. The particulars concerning the patient are not given, but the oil was a "cineol eucalyptus oil" and a good preparation of the kind.

Case XIX.—Orr (1906) stated that a boy, two years and nine months old, took 2 drachms of the oil and was seen 15 minutes later. He was in collapse, unconscious, had a very rapid pulse, and his breathing was stertorous. The pupils were contracted to pin-points. He vomited early and was purged. Zinc sulphate was given and was followed by emesis. Whiskey and coffee were then given. One hour later consciousness had returned and the patient was well.

Case XX.—Benjamin (1906) records the case of a boy, eight years of age, suffering from intermittent fever, who was given 6 drachms of eucalyptus oil at 5 a. m. He vomited half an hour later. At 7 a. m. he became unconscious; vomiting recurred several times before 11 a. m. At this time he was found in partial collapse, the pupils were contracted and the breathing labored. The temperature was 99.8° and the pulse 128. The abdomen was tympanitic. Hiccough was troublesome.

The treatment consisted of cold applications to the head, mustard on the neck, an ammonia mixture internally, and enemata. At 3 p. m. the patient regained consciousness. No after-effects were noted.

CASE XXI.—Myott (1906) observed a man, 34 years old, a heavy drinker, who took 6 drachms of eucalyptus oil. He walked about for two hours, then became dazed and suddenly fell unconscious. Warm water was introduced into the stomach and the patient vomited. Four hours after ingestion of the oil, he was cyanotic and the breathing was labored. Frequent attempts to empty the bronchial tubes of a thin frothy secretion were made. Pulse 128, respiration 24, temperature 97°. Pupils slightly contracted. The patient was then given strychnin and oxygen. The expectoration became thick and blood-tinged, the fever rose continuously, and 40 hours after ingestion, just prior to death, the temperature was 103°, pulse 140, respirations 48. The autopsy showed bulky, heavy lungs, some gastritis and some pleuritis.

CASE XXII.—Schroeder (1908) stated that a child one and one-half years old exhibited evidence of delirium, coma, vomiting and collapse after an unknown dose of eucalyptus. Recovery was complete in a few hours.

CASE XXIII.—Robertson (1909) reported that a man, 55 years old, took 5 drachms of eucalyptus oil before retiring. He wakened during the night feeling sick, but did not vomit until several hours later. He was terribly prostrated, pale grey in color, and cold to the touch. The pulse, however, remained normal in rate and rhythm. The following afternoon he felt fairly well, and he returned to work within a few days.

CASES XXIV AND XXV.—Kirkness (1910) reports two cases:

(1) Man, 28, took between 2 and 3 drachms of eucalyptus oil. Ten minutes later, he suffered from dizziness and from marked dyspnœa. The pupils were dilated and the pulse was weak and thready. The temperature sank to between 95° and 96° F. The patient vomited and complained of a sensation of girdle-like constriction. The skin was greenish-yellow. He complained of drowsiness, of great coldness, and of intense frontal and occipital headache. Half an hour after ingestion, marked diarrhœa set in and also frequent and painful micturition. The fæces were dark in color and smelled of the oil. He was given emetics and stimulants, was put to bed and was surrounded with artificial heat. This treatment was followed in a few hours by a return of normal temperature and pulse. For three days, however, he looked chlorotic and showed an ataxic gait. The fæces, urine and breath all smelled of the oil for a fortnight after the poisoning. Recovery was complete.

(2) A girl of 18 years took 1 ounce of the oil. She complained of intense headache and vomited. She showed collapse, bodily and mentally. The pulse became very feeble, the temperature subnormal, and the pupils dilated. She also complained of a girdle-like constriction. She recovered.

CASE XXVI.—Allan (1910) recorded a case of a child, 20 months old; eucalyptus oil was applied to its chest and 1 ounce of the oil was given by mouth. Within 20 minutes, the child became very sick and seemed to suffer violent pain. A few minutes later, it became semi-comatose and vomited. The pulse was feeble and intermittent, the temperature subnormal; the patient collapsed. Stimulants and artificial heat were employed and two days later the child was reported as well.

CASE XXVII.—Jolly (1910) describes a patient, admitted to the hospital for anæmia and dyspepsia, who was found to be suffering from ankylostomiasis. Magnesium sulphate was given at night, followed next morning by eucalyptus oil min. xxx, chloroform 45 min. and castor oil 10 ounces in two doses. Two hours later the patient was weak and giddy, and an hour later in collapse. Langour, giddiness, dyspnœa, general pains (most severe in the head, abdomen and urethra) were complained of. The respiration became shallow and labored, the pulse weak and irregular, the blood-pressure low, and the pupils dilated. The breath and skin smelled of eucalyptus. Vomiting did not occur; no urine or fæces passed. Following the application of a mustard plaster over the heart and the administration of strychnine, atropine, artificial heat and enemata, recovery occurred.

CASE XXVIII.—Foggie (1911) reported the case of a boy six years of age, who took 1 drachm of the oil. Four hours later nausea and vomiting occurred, the patient passing into a serious condition of coma and collapse. The case was treated as though it were one of opium poisoning and the recovery was complete.

CASE XXIX.—In 1914, Winterbotham reported a case of poisoning by oil of eucalyptus. The patient, a man 30 years old, took a teaspoonful of "the best eucalyptus extract" at 7 a. m. and another at 10 a. m. He noticed no effect until after luncheon, when (at 1.15 p. m.) he became very pale, began to sweat profusely, and became unable to walk without assistance. He felt drowsy, and retched a little. There was no vomiting and no headache. Winterbotham saw him at 3.30 p. m., and could detect the odor of eucalyptus on his breath. The gait was unsteady. Now and then, his talk was nonsensical. The articulation was impaired. The pulse, though weak, was not accelerated. Alcoholic intoxication was ruled out. At 4 p. m., the patient went to sleep and slept heavily until the next morning when he awoke feeling perfectly well.

Thus, in the above 29 cases, found in the literature, seven ended fatally; all of the other patients appear to have recovered completely within a few days.

Only five cases of the second class of cases could be found; that is, of instances in which the patient responded in an unexpected and unaccountable manner to minute or therapeutic doses. These cases are particularly interesting in relation to the one we report.

CASES XXX AND XXXI.—Galewsky (1905) reported two cases in which a skin disease developed as the result of the patient coming in contact with branches of the eucalyptus tree. He asserted that dermatitis not infrequently results after rubbing eucalyptus oil into the skin and he cited one instance in which an acute papular dermatitis followed its use.

Galewsky states that he was consulted by a woman suffering from erythematous urticaria. She presented large and small urticarial lesions and the intervening areas showed erythematous spots. The itching was intense and the disease was of long duration. The exposed cutaneous surfaces were particularly involved, but the neck and breast also, though to a less degree. She asserted that this rash would entirely disappear when she was away from home for a considerable length of time, but always reappeared on her return. She stated also that the itching was always more severe when she remained for any length of time in one particular room. Galewsky visited her home and in the above-mentioned room he found branches of the eucalyptus used as an ornament. Thinking that this might possibly be the etiological factor, he ordered it removed. The housemaid scoffed at this idea and to prove the harmlessness of the eucalyptus, moistened some of these leaves and rubbed them on her own skin. At the end of half an hour she exhibited lesions identical with those complained of by her mistress. The eucalyptus was removed and subsequently both patients fully recovered, the rash never reappearing.

CASE XXXII.—Davies (1906) stated that his son fainted on inhaling the vapor of eucalyptus and that on another occasion he had to leave a chapel during service on account of a threatened fainting spell brought on by the odor of eucalyptus, the leaves being used in the way of decoration. This peculiarity is stated to be inherited from the mother who also faints on smelling eucalyptus.

CASE XXXIII.—Hans Vörner (1907) reported an experience with eucalyptus which proves conclusively that in certain persons

it can produce skin lesions. In August, 1906, a patient entered the skin clinic and stated that for two days he had been taking 20 drops of eucalyptus oil and that, after doing so, he had developed a skin rash which itched and burned. He ascribed this to the eucalyptus. On examination, it was found that wheals were present over the entire cutaneous surface. They were chiefly discrete, but in places were confluent. The single lesions varied from 2 mm. to 2 cm. in diameter, while the confluent lesions were in some areas as large as one's hand. They were of a livid red color, the center sometimes slightly blue, and the edges a more intense red. The oil was stopped and the rash promptly disappeared. In order to test the assertion of the patient, the oil was administered again 10 days later, whereupon an identical rash appeared within 24 hours.

Six weeks later the rash reappeared without any oil having been administered. The patient complained, however, of a cold in the head, of headache, and of an intense taste of eucalyptus oil. Identical attacks recurred in November and again in December. For two or three months he remained free, but similar attacks occurred again in March and again in April, but the taste of oil was not present in these last two attacks.

During the various attacks the back of the head, the back, abdomen, right breast, arm, thigh and legs were all involved, the hands and feet escaping altogether except for a lesion on one thumb during one of the attacks.

Case XXXIV.—Oppenheim (1912) reported that a tailor, 36 years of age, complained of skin lesions developing as the result of taking cough lozenges ("*Huste nicht*"). The backs of the hands, palms, fingers, wrists, and dorsa of the feet showed an eruption, consisting of pea-sized, bright red, cherry-red and brownish-red papules and nodules. These were mostly circumscribed, but were confluent on the fingers and toes, and on the palms and soles of the feet. The color did not disappear on pressure with the glass slide. Hæmorrhages appeared here and there. There was no desquamation. The mucous membranes were not involved. Slight itching was associated with the eruption. The color changed later to brown. The rash was preceded by anorexia, insomnia, malaise and fatigue, those symptoms appearing two hours after the last tablet was taken.

Discussion

From the preceding analysis, at least two different syndromes emerge as evidences of intoxication with derivatives of myrtaceous plants (eucalyptus oil, myrtol, cineol, etc.), and we shall venture to designate them respectively as (1) a myrtogenic neuropathy and (2) a myrtogenic dermatopathy, though without prejudice as to whether the terpenes in the oils are the toxic agents or some chemical substance that accompanies them. The dermatopathy may in some of the cases be a special instance of the neuropathy, through the mediation of the autonomic nerves innervating the blood vessels of the skin, though a true dermatitis seems certainly to have been present in other cases.

(1) *The Myrtogenic Neuropathy.*—In the cases discovered in the literature, the first 29 grouped as Class I (*vide supra*) appear to belong to this category. In a few minutes, or a few hours, after the ingestion of a considerable quantity of the myrtaceous derivatives mentioned, the patients became seriously ill. They were pale, dyspnœic, and restless and complained of headache, dizziness, twitchings, and of pains (in the chest or limbs). At first, the intellect was sometimes clear, but, in many instances, the patients soon became drowsy and complained of feeling dazed and of a loss of knowledge of the whereabouts of their extremities. On attempting to walk, they staggered about and sometimes fell. Some patients stated that they felt a girdle-sensation (constriction). In the severer intoxications, they were delirious or suffered from convulsive seizures, and some became comatose, with pronounced symptoms of collapse (tachycardia, arterial hypotension, pallor and slight cyanosis, cold extremities, diminished reflexes, hypothermia). Vomiting and diarrhœa were common accompaniments of the intoxication. It is fortunate when these symptoms occur, and if vomiting does not occur spontaneously, it should be induced, or the stomach should be washed out to prevent further absorption of the poisonous substance.

The behavior of the pupils has been variable; in most cases, there was extreme myosis; in some instances, outspoken mydriasis was observed. It seems likely that the myosis indicates an irritation of the midbrain autonomic system, the mydriasis a paralyis of the same. In the domain of the pelvic division of the cranio-sacral autonomic system, the patients sometimes complained of pollakiuria and of dysuria.

The pleural effusion reported in two of the cases deserves especial mention; in Neal's case, a quart of fluid was found in the pleural cavities; in Lewin's case, a bloody effusion was observed. Whether these pleural phenomena were accidental accompaniments, or were actually due to the intoxication, must be left to later studies to decide.

Several observers have been struck with the resemblance to poisoning by opium, but they emphasize the absence of the stertorous breathing that accompanies that intoxication.

(2) *The Myrtogenic Dermatopathy.*—In four cases in the literature, and in the case we report ourselves, remarkable cutaneous manifestations followed the ingestion of myrtaceous derivatives. In our own case, the skin lesions were associated with marked nervous symptoms (great depression; symptoms of collapse).

The lesions in the skin vary in their nature. Sometimes merely (1) *erythematous;* sometimes they are (2) *urticarial* in type; and sometimes there is (3) an outspoken dermatitis.

Conclusions

(1) Derivatives of plants belonging to the natural order *Myrtaceæ,* and especially oil of eucalyptus and myrtol, may in large doses cause profound intoxication. In certain persons, there is an idiosyncrasy, the symptoms of intoxication occurring after minute or therapeutic doses.

(2) The intoxication may affect chiefly the nervous system (*myrtogenic neuropathy*) or chiefly the skin (*myrtogenic dermatopathy*); in some persons, nervous and cutaneous manifestations are simultaneously observable.

(3) Recovery occurs in most instances, though several fatalities following eucalyptus poisoning have been reported.

(4) The symptoms of intoxication of the nervous system observed in man can be reproduced in animals by subcutaneous and by intraperitoneal administration of myrtol.

LITERATURE

Allan, J.: Poisoning by oil of eucalyptus. Brit. M. J., Lond., 1910, I, 569.

Benham, F. L.: Two cases of acute poisoning by oil of eucalyptus. Lancet, Lond., 1905, II, 1894.

Benjamin, J.: Eucalyptus poisoning. Brit. M. J., Lond., 1906, I, 1020.

Davies, H. R.: Eucalyptol and "fainting"; a warning. Lancet, Lond., 1906, I, 403.

Foggie, W. E.: Eucalyptus oil poisoning. Brit. M. J., Lond., 1911, I, 359.

Galewsky: Ueber Eucalyptus-Dermatitiden. Dermat. Ztschr., Berl., 1904, XII, 36-38.

Jolly, G. G.: A case of poisoning by eucalyptus oil. Indian M. Gaz., Calcutta, 1910, XLV, 458.

Kirkness, W. R.: Poisoning by oil of eucalyptus. Brit. M. J., Lond., 1910, I, 261.

Myott, E. C.: Case of eucalyptus poisoning. Brit. M. J., Lond., 1906, I, 558.

Neale, A.: Case of death following blue gum (*Eucalyptus globulus*) oil. Australas. M. Gaz., Sydney, 1893, XII, 115.

Oppenheim, M.: Ein durch Eukalyptusbonbons hervorgerufenes Exanthem. Dermat. Wchnschr., Leipz. u. Hamb., 1912, LIV, 224-226.

Orr, J.: Eucalyptus poisoning. Brit. M. J., Lond., 1906, I, 1085.

Owen, F. J.: Notes of a case of poisoning by eucalyptus. Austral. M. J., Melbourne, 1885, N. S., VII, 394-397.

Robertson, K.: Overdose of eucalyptus oil. Brit. M. J., Lond., 1909, I, 1297.

Schröder: Vergiftung mit Eukalyptusöl. Aerztl. Sachverst.-Ztg., Berl., 1908, XIV, 153.

Sheaf, E.: Toxic action of extract of eucalyptus. Brit. M. J., Lond., 1888, I, 849.

Smith, F. A.: Chemical examination of a eucalyptus oil, an overdose of which caused death. Merck's Report, N. Y., 1906. XV, 231.

Taylor, H. S.: A case of acute poisoning by eucalyptus oil. Lancet, Lond., 1905, II, 963.

Thomas, E. H.: A case of eucalyptus poisoning in an infant four weeks old. Indian M. Rec., Calcutta, 1899, XVII, 502.

Vörner, H.: Durch Eukalyptusöl hervorgerufenes Exanthem, das später periodisch recidivierend wird. Dermat. Ztschr., Berl., 1907, XIV, 678-681.

Winterbotham, L. P.: Eucalyptus oil poisoning. Med. J. Australas., Sydney, 1914, I, 129.

DAKIN'S SOLUTION AND DAKIN'S OIL IN THE NORMAL PERITONEAL CAVITY OF THE DOG

By ERNEST G. GREY, M. D.

(From the Surgical Division of the Hunterian Laboratory of The Johns Hopkins University)

The following observations are reported in order to draw attention to the fact that the indiscriminate use of the chlorin antiseptics is not entirely devoid of danger. It must be emphasized, however, that in presenting them no criticism is suggested regarding the Carrel-Dakin method of wound treatment or the use of Dakin's oil, inasmuch as clinical experience abroad, in The Johns Hopkins Hospital and in certain other institutions in this country, has shown the importance of these antiseptics in combating infections.

The remarkable results from the use of the normal solution of chlorinated soda reported by Carrel,[1] and from the use of the dichloramine-T oil reported by Lee and Furniss[2] suggested these agents in certain infections of the pleural and peritoneal cavities. Sufficient time has elapsed now since the introduction of the chlorin antiseptics in the treatment of empyema to justify the conclusion that both agents may be used with safety in an infected pleural cavity. The evidence at present, however, regarding the reaction of the infected peritoneum to Dakin's solution and to dichloramine-T oil, is much less definite.

The question as to whether a particular germicide should be used in infections of the serous cavities, of course, may be settled more or less satisfactorily either by observing the effects resulting from the use of the antiseptic in selected clinical cases or by studying the reaction of animals injected with it under varying conditions. The latter method has the disadvantage that it is difficult, in fact often impossible, to reproduce the same pathological process in animals. This means that the conclusions drawn from animal experiments must be used with a considerable amount of reservation when they are applied to clinical work. Laboratory experiments, nevertheless, may be of great service in working out problems of this nature, since it is only by experimenting with animals that we may determine how the normal serous membranes will react to a given chemical agent.

With this idea in mind certain problems were studied in the laboratory shortly after the introduction of the Carrel-Dakin method of wound treatment into this hospital, and again later when the dichloramine-T oil technique was adopted for suitable cases. The excellent results obtained with the chlorin antiseptics suggested to Dr. Halsted several possible uses for them in appropriate cases of intra-abdominal infections. In the following paragraphs a brief review of the experiments will be outlined.

Dogs apparently in good health were used throughout the work. The solutions of chlorazene were obtained by dissolving the commercial tablets (Abbott) in sterile water. The hypochlorite solution (Dakin's solution) came from the hospital pharmacy. A fresh preparation was made each day. In all

[1] Carrel, Dakin, Daufresne, Dehelly et Dumas: Traitement abortif de l'infection des plaies, La Presse méd., 1915, XXIII, 397.

[2] Lee, W. E., and Furniss, W. P.; The Use of Dichloramine-T in the Treatment of Infections and Infected Wounds, Ann. Surg., 1918, LXVIII, 14.

of the experiments with Dakin's oil a 5 per cent solution of dichloramine-T in chlorinated paraffin oil (chlorcosane) was used.

In the first series a solution of chlorazene was injected into the peritoneal cavity with a Record syringe. One animal weighing 17 pounds received 30 c. c. of a .5 per cent solution. Forty-eight hours later the dog was active and ate well. When the abdomen was opened, however, about one and a half ounces of grayish-colored, free fluid were discovered. There was a moderate and general congestion of the peritoneal surfaces with a rather marked deposit of fibrin on the viscera in the part of the cavity which was nearest to the point of injection.

Another dog (weight 21½ lbs.) received 20 c. c. of a 1 per cent solution. Eleven days later it died and at necropsy the abdomen was found to be full of fluid. Fibrin was present in large amounts. Throughout the four quadrants, but particularly in the upper two, loops of bowel were glued together by the exudate. Both the parietal and the visceral peritoneal surface were greatly altered in appearance.

The results in another dog (weight 56 lbs.) may be mentioned. In this case 90 c. c. of a 1 per cent solution were injected intraperitoneally. Six days later the abdomen was opened under aseptic precautions. About 250 c. c. of cloudy, blood-stained, free fluid were found. A considerable amount of fibrin was present, and the peritoneal surfaces were thickened and deep red in color.

Practically all of the fluid was removed and the wound closed. The animal made a rapid recovery and 16 days later when the viscera were again inspected almost nothing was found to supply evidence of the former inflammatory changes. The dog undoubtedly would have died had the fluid not been removed, as clinically it showed a progressive loss of appetite and strength up to the time of the first exploratory operation.

In the second series Dakin's solution was used. No animal succumbed to the effects of the fluid injected in amounts less than 30 c. c. One dog (weight 15½ lbs.) received 30 c. c. intraperitoneally, and at the end of the following week it was active and had a good appetite. An exploratory incision, made eight days after the injection, revealed only a few cubic centimeters of free fluid. There was still a slight congestion of the visceral peritoneal surfaces. A few traces of old fibrin were evident at certain points. The picture at this time was not far from the normal; it indicated, nevertheless, that there had been a marked reaction to the injection. The cause of death remained obscure.

Into another dog (weight 18 lbs.) 90 c. c. were injected intraperitoneally. Fluid rapidly accumulated and death occurred on the eighth day. The pathological picture was similar to that noted in some of the fatal cases described above. Larger amounts of the neutral solution of chlorinated soda led to a more rapid exitus with extensive peritoneal changes.

A striking feature of an injection performed without anesthesia was the evidence of severe abdominal pain. A few cubic centimeters of the fluid sufficed to cause marked abdominal rigidity, extensor spasms of the leg muscles, involuntary defecation and urination, and extreme restlessness.

Approximately similar results from the injection of Dakin's solution into the normal peritoneal cavity have been reported recently by Mann and Crumley.[3]

In a third series of animals an attempt was made to determine how the normal gall-bladder and common bile-duct would react to an injection of Dakin's solution. One experiment consisted of exposing the gall-bladder under aseptic precautions and aspirating all of the bile with a Record syringe. Through the same needle-hole the bladder was then distended with Dakin's solution (60 c. c. were used) after which the puncture wound was closed with fine silk stitches. This animal was in excellent condition several days later. An exploratory incision made 4 days after the operation disclosed no evidence of peritoneal reaction.

In a number of other dogs a fistula was established between the gall-bladder and the skin by transplanting a piece of jejunum (measuring about 7 cm. in length) with its blood supply intact, in such a way that one end opened into the gall-bladder and the other upon the surface of the abdomen. After the wounds had healed Dakin's solution was injected into the gall-bladder through the intestinal lumen. No deleterious effects were ever noted subsequent to such injections.

A fourth series of experiments was carried out more recently with Dakin's oil. One dog (weight 22 lbs.) received 11 c. c. intraperitoneally. There was an immediate reaction to the oil. The animal became restless and when placed on the floor a marked, cat-like arching of the spine was noted together with an extensor rigidity of the hind legs. About half an hour later it vomited and gave evidence of much abdominal discomfort. The animal died 26 days after the injection, greatly emaciated. Following the introduction of the oil the dog continued to remain quite ill. There was marked weakness together with anorexia and some vomiting. At autopsy no signs of an active inflammatory process were evident, but there was ample evidence that a very extensive process of this nature had existed in the near past. The loops of intestine were inextricably matted together, and in the vicinity of the site of the injection there was an indurated mass which suggested an old inspissated abscess.

Into the peritoneal cavity of another dog (weight 20½ lbs.) 20 c. c. of the oil were injected. The animal died during the following night and when the abdomen was opened a typical picture of extensive peritonitis appeared. Besides the free fluid, the fibrin and the congestion of the peritoneum, there was a perforation with ragged necrotic edges on the anterior surface of the stomach. Most of the oil injected had come in contact with this region first.

In order to ascertain the effects of the oil upon the gall-bladder and common duct all of the bile was aspirated from the bladder and a corresponding quantity (16 c. c.) of

[3] Mann, F. C., and Crumley, W. G.: Neutral Solution of Chlorinated Soda (Dakin's solution) in the Normal Peritoneal Cavity, Jour. Amer. Med. Assoc., 1918, LXX, 840.

the dichloramine-T was then injected into it. The needle-hole was closed with fine silk stitches. Two days later the dog appeared to be normal in every way. The animal was sacrificed on the 43d day and on examination gave no evidence of an old peritonitis. Both the common duct and the duodenal mucosa were natural in appearance. The gall-bladder, however, was shrunken and contained some thick, yellowish mucus.

In the concluding experiments Dakin's oil was injected into the right pleural cavity. One dog (weight 45 lbs.) received 16 c. c. No anesthesia was used. There was an immediate and marked reaction—restlessness, evacuations of the bladder and rectum, muscular spasm of the abdomen, and a certain degree of extensor rigidity of the legs. The animal was placed on its feet after the injection but soon fell to the floor. It died with symptoms of respiratory failure 2½ minutes after the first few cubic centimeters of oil had been injected. When the thorax was opened, several large, dry, whitish areas on the pleura were found, which suggested in a way superficial silver nitrate burns. The oil lay at the bottom of the cavity. The clinical course here strongly reminded one of the pleural reflex deaths described particularly by French writers.

Ten cubic centimeters of the oil were injected into the pleural cavity of another dog of about the same weight. In this instance the animal was anesthetized. No unusual symptoms marked the convalescence, and the animal remained apparently in good health.

CONCLUSIONS.

Both the neutral solution of chlorinated soda (Dakin's solution) and dichloramine-T in chlorinated paraffin (Dakin's oil), when injected into the normal peritoneal cavity of a dog, lead to an inflammatory reaction, the degree of which is directly proportional to the amount of chlorin antiseptic used. With a sufficient quantity (less of the oil suffices) death ensues.

When either of the chlorin antiseptics is injected into the gall-bladder of a dog no abnormal symptoms appear. Following the injection of the oil, however, the gall-bladder becomes thickened and shrunken, though the remainder of the biliary tract shows no discernible changes.

A small amount of Dakin's oil, when injected into the normal pleural cavity of an unanesthetized dog, may lead to a rapid (reflex?) death.

Since Dakin's oil, particularly, has been used without recognizable ill effects in certain infections of the abdominal cavity, the results from the experiments outlined above suggest that the wall of an abscess cavity or sinus must play an important part in protecting the peritoneum in general from the effects of the free chlorin. They also suggest that the maintenance of an adequate drainage tract is an indispensable part of the technique for using antiseptics of this nature within the abdomen. Until more evidence is at hand, then, both of the chlorin antiseptics should be used in intra-abdominal infections with caution and certainly only in carefully selected cases.

MULTIPLE PRIMARY MALIGNANT TUMORS

WITH REPORT OF A CASE OF CARCINOMA AND SARCOMA IN THE SAME INDIVIDUAL

By RALPH H. MAJOR

(From the Department of Pathology, University of Kansas School of Medicine, Rosedale, Kansas)

The presence of multiple tumors in the same individual has been for many years a subject of much interest. It was early noted and subsequently emphasized that with certain kinds of tumors the tumor formation was more often multiple than single. Virchow (182) called attention to the presence of multiple fibromata of the skin and v. Recklinghausen (137), with whose name this condition has been since associated, made extended studies of this disease. These two observers also noted that such multiple tumors sometimes underwent malignant degeneration and were transformed into sarcomata. Later, similar cases were reported by Genersich (54), de Morgan and Coupland (115), Westphalen (191), and others. Another well-known type of multiple tumors is that of multiple lipomata which have been studied especially by Meerbeck (110), Blaschko (21), Petren (128), Weil (192), and Lyon (105). In addition to these examples it has been noted that certain other benign tumors such as angiomata may be often multiple, and a patient may have angioma of the liver, adrenals, ovaries and uterus, as in a case reported by Payne (125).

The presence of multiple malignant tumors is, however, comparatively uncommon and the following case is reported as an example of this interesting condition.

Mrs. H. G. age 60 years was admitted to the Bell Memorial Hospital April 19, 1915 suffering with a tumor on the face. This growth, which involved the right side of the nose and extended to the inner canthus of the right eye, had been present for several years and was growing slowly (Fig. 1). The clinical diagnosis of rodent ulcer was made and X-ray treatments of the growth instituted. While in the hospital the patient complained a great deal of headache, had little appetite and at times talked irrationally. Death occurred rather unexpectedly on May 22, 1917, and the autopsy was performed two hours later.

The autopsy showed a marked bronchopneumonia of both lungs, a generalized arteriosclerosis and extensive scarring of both kidneys. The most interesting findings were those in the stomach. The wall of the stomach was markedly thickened throughout, had a whitish semi-translucent appearance and cut easily. At the cardia of the stomach there was a large polypoid

growth which showed some areas of ulceration on the surface. This mass also had ulcerated through the wall of the stomach in one place, forming a sinus which passed by the spleen and through the diaphragm to the base of the left lung where it was closed by dense adhesions. No metastases were noted.

The microscopic examination of the tumor in the stomach shows it to consist of masses of round cells, presenting no especial arrangement and showing a small number of connective-tissue fibrils (Fig. 2). Microscopic sections of the tumor of the face show it to be composed of large atypical epithelial cells arranged in nests and strands. In some areas there are epithelial pearls present and evidence of infiltration downward (Fig. 3).

The gross and microscopic evidence in this case shows that we are dealing with an example of two quite different types of malignant tumors in the same individual—a carcinoma of the face and a round-celled sarcoma of the stomach.

The presence of two primary malignant growths in the same person was at one time considered extremely rare, Orth stating in 1895 (123) that he had never seen a carcinoma and a sarcoma in the same individual. In 1896 Walter (184) collected six cases in each of which the two tumors were of different types. Wells (190) in 1901 collected 17 cases of multiple primary tumors and three cases of tumors composed of transformed epithelium and mesoderm in the same organ, the so-called carcinoma sarcomatodes. Wooley (195) in 1903 collected 26 examples of multiple primary carcinomata, five of multiple primary sarcomata and four cases of multiple malignant growths of more than one type. Theilhaber and Edelberg (173) in 1912 made a very extensive study of multiple primary carcinomata, collecting 44 examples of multiple carcinomata in the same system of organs and 41 cases of multiple carcinomata in various organs. Bartlett (9) in 1914 in an excellent article on the subject states that he has reviewed 95 cases of multiple primary tumors. All of these observers, however, have emphasized the comparative rarity of the condition, although statistics upon this point show some variation. Reichmann (139) in 711 necropsies found two examples, Redlich (138) in 507 cases saw two, Goetting (56) in 1000 postmortems found only two instances.

Some observers, notably Walter (184), Wooley (195), and Adami (3), attach much importance to the occurrence of multiple primary tumors as shedding some possible light upon the etiology and distribution of malignant tumors, whereas other investigators, notably Wells (190), considered them more in the light of a coincidence. In order to assist in the understanding of this interesting problem, a collection of cases has been made and the various facts as to the location, number, and nature of the tumors considered.

In all 628 examples of multiple primary tumors have been reviewed. The greatest number of these cases, 389, were examples of multiple carcinomata in the skin, in the same organ or in each of a pair of organs. This group of tumors has been thoroughly studied by Theilhaber and Edelberg (173) and as their tables are so comprehensive no attempt has been made to add to their collection.

Tabulations of carcinomata in different organs but belonging to the same system show 43 examples, while carcinomata in various organs not members of the same system of organs were present in 53 instances. In all then 485 instances of multiple primary carcinomata were collected.

The number of instances in which examples of different types of tumors were found in the same person was much smaller. One hundred and twenty-three such cases were noted, in 66 of which the tumors were in the same organ, in nine they were in organs belonging to the same system and in 48 cases the different tumors were located in various organs. In this group it is of interest to note that in over one-half of the cases (54 per cent) the different types of tumors were located in the same organ. The uterus was the most common seat of two tumors of different types, being represented by 22 instances, followed by the breast and the thyroid gland, each showing 10 examples.

The most common combination of different types of malignant tumors was that of carcinoma and sarcoma. Ninety-two instances of this combination were noted, 62 or 75 per cent of which were located in the same organ, seven were located in the same system and 23 in different organs.

The presence of both carcinoma and sarcoma in the same organ has led to much discussion especially since the work of Virchow * who laid stress upon the carcinoma sarcomatodes, a tumor in which both carcinomatous and sarcomatous elements are present.

Wells * until 1901 found only three undoubted instances of such tumors. A large number have been described since that time, but these figures have been greatly reduced by Herxheimer (70) who states that the actual number of cases of true carcinoma sarcomatodes reported up to 1908 was 20. Herxheimer pointed out that many cases reported in the literature as instances of carcinoma sarcomatodes are really examples of two distinct tumors, a carcinoma and a sarcoma in the same organ. Saltykow (150) in 1914 stated that there were 25 authentic cases reported in the literature to which number he added three. In our table, because of the difficulty of separating them, the cases of carcinoma sarcomatodes are included with those in which a carcinoma and a sarcoma were present as distinct tumors in the same organ.

This brief summary of the cases of multiple primary tumors would seem to indicate rather clearly that no single explanation suffices in all cases and that although some instances may be explained as simple coincidences, in certain others deeper causes are at work.

In the examples of multiple primary carcinomata of the same organ or of adjacent organs we are probably dealing with two factors—transmission by infection and multiple origin of tumors. Many cases are now on record indicating that contact may spread a carcinoma from a primary growth to an adjacent organ. Such tumors have been described especially in the skin and Borrmann (24), who has devoted much study to this problem, although believing that the number of cases

* *Loc. cit.*

FIG. 1.—Patient on Admission.

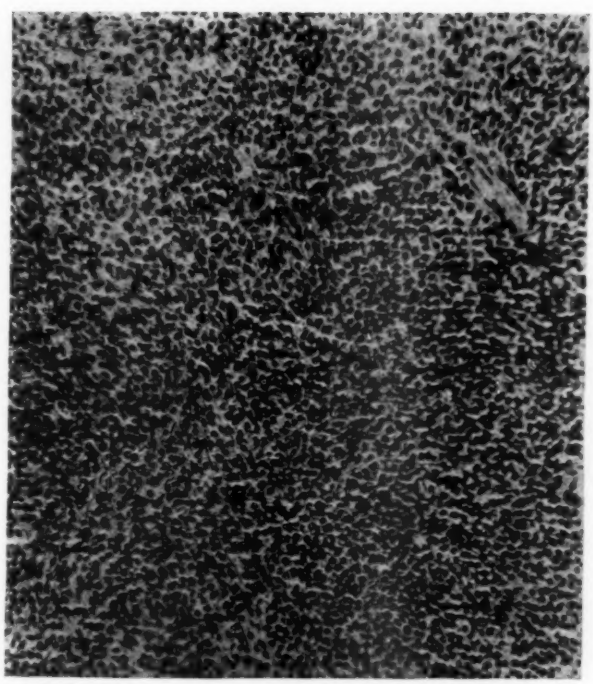

FIG. 2.—Microscopic Section of Stomach Tumor. Zeiss obj. AA, oc. 4. Haematoxylin and Eosin.

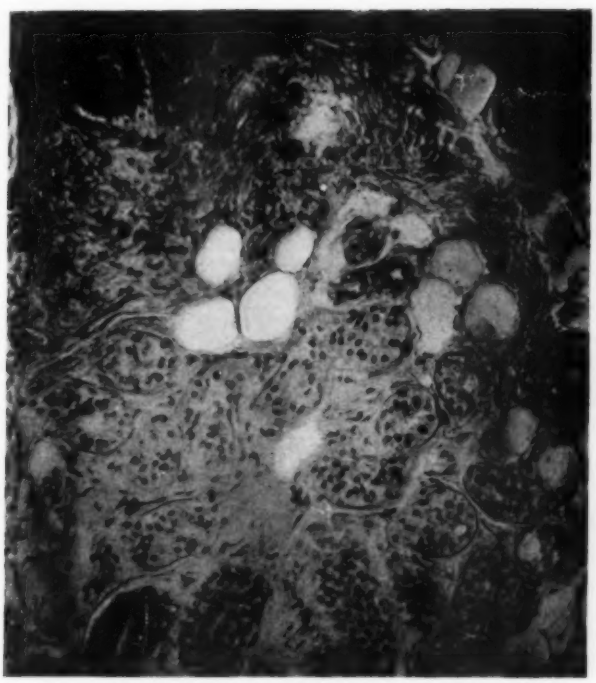

FIG. 3.—Microscopic Section of Face Tumor. Zeiss obj. AA, oc. 4. Haematoxylin and Eosin.

of transplantation carcinomata (Impfkarzinome) has been exaggerated, yet admits its occurrence. This group of cases, although many of such growths are often apparently secondary to a primary tumor, are in many instances possibly not ordinary true metastases, since the transference of the growth may conceivably be accomplished in some other manner than by an actual implantation of tumor cells.

The multiple origin of carcinomata is now, since the work of Peterson (126) and of Hauser (67) a well-established fact. Both of these observers have shown that carcinomata may arise simultaneously from several centers of origin. While disagreeing as to the relative frequency of the "unicentric" and "multicentric" mode of origin, both agree that the "multicentric" mode does occur. Thus a carcinoma may, like an abscess, arise as a single large lesion, or it may be formed by coalescence just as a number of small abscesses may fuse to form a larger lesion; or again the multiple carcinomata may remain discrete just as we often observe multiple small abscesses. Some of the most striking examples of the multicentric origin of malignant tumors are those in which a certain number of polypi, in cases of multiple polyposis of the stomach and intestine, become malignant and are transformed into carcinomata. Ribbert (142) has collected 30 such cases.

The presence of different types of tumors in the same organ such as a carcinoma and a sarcoma, or the presence of a mixed type as the carcinoma sarcomatodes, while often regarded as a mere coincidence, has taken on an added interest and importance since the oft-quoted work of Ehrlich and Apolant (40). These two observers by repeated inoculation of a typical adenocarcinoma in mice succeeded in changing it first into a mixed tumor, and later into a typical sarcoma. Russell (148) has reported an adenocarcinoma of the breast in a mouse, which after continuous growth in the animal gradually became sarcomatous and later became a pure sarcoma. This change of the carcinoma into a sarcoma in Russell's case seems to be controlled entirely by the time element, since if the transplanted carcinoma is removed early and transmitted to another animal, carcinoma results, whereas if the transplanted carcinoma is allowed to grow until it becomes a sarcoma, all animals then inoculated develop a pure sarcoma.

These experimental findings combined with clinical observations suggest very strongly that the presence of a carcinoma and sarcoma in the same organ is due to some abnormal stimulus which acts upon both epithelial and mesodermal elements, producing either both epithelial and mesodermal tumors or a single tumor showing both types of cells, as in the carcinoma sarcomatodes. Similar influences are probably at work in such cases as that reported by Kidner (83) where the removal of a sarcoma was followed later by the appearance of a carcinoma at the site of the old operation.

Our statistics show that the multiple tumors do not have a predilection for organs of the same system excluding paired organs, which is in marked contrast to their predilection for a single organ. We have found multiple tumors—both carcinomata and tumors of different types—more common in organs not related by any system. The occurrence of multiple tumors in various organs cannot be readily explained, but here again the assumption of more than a mere coincidence would seem to be justified in many instances. The susceptibility of individuals of certain families to malignant tumors such, for instance, as those related by Vander Veer (180), is an old clinical observation, which seems now to be placed upon a firm base by the brilliant breeding experiments of Slye (164). She has shown that mice with a cancerous ancestry have a marked tendency to develop spontaneous cancers, and also that mice with such ancestry develop carcinomata readily as the result of a trauma which in control animals having a non-cancerous ancestry produces no such results. The suggestion here is rather strong that individuals developing multiple malignant tumors have some sort of a susceptibility to tumors which is not limited to any one organ or region of the body.

There must also be mentioned the possibility that in a few of the cases we are dealing not with multiple primary tumors, but with a carcinoma, the metastases of which simulate very closely sarcomata. Such instances have been reported by Polano (132). The number of such cases, however, is probably very small.

Nine examples of three primary multiple tumors were noted and two examples of four tumors occurring simultaneously. The case of Lewis (100) is unique; he reported nine different tumors in the same patient, while that of Sliwinsky (163) who described seven is equally interesting.

In our own case it is difficult perhaps to draw any very definite conclusions from the presence of two distinct and different tumors. They might be regarded simply as a coincidence, although the case would seem to be equally well explained by the assumption that the patient was predisposed to cancer and that subsequent irritation in two organs produced malignant growths in both of them. A great variety of combinations of two different tumors are obviously possible, but this is the only instance noted in which the combination of a carcinoma of the face with a sarcoma of the stomach occurred.

MULTIPLE CARCINOMATA IN THE SAME SYSTEM OF ORGANS

Abesser	(2)	Carcinoma of jejunum, carcinoma of tongue.
Beadles	(10)	Carcinoma of breast, epithelioma of cervix.
"		Carcinoma of breast, epithelioma of vulva.
Besche	(17)	Carcinoma of jejunum, carcinoma of colon.
Böckel	(22)	Carcinoma of uterus, carcinoma of breast.
Borchhardt	(23)	Carcinoma of stomach, carcinoma of colon.
Bucher	(27)	Carcinoma of stomach, carcinoma of descending colon.
Devis	(37)	Carcinoma of pylorus, carcinoma of rectum.
Eichbaum	(41)	Carcinoma of esophagus, carcinoma of stomach.
d'Erchia	(44)	Adenocarcinoma of labia, squamous-celled carcinoma of cervix.
Feilchenfeld	(45)	Carcinoma of stomach, carcinoma of rectum.
"		Carcinoma of stomach, carcinoma of gall-bladder.
"		Carcinoma of stomach, carcinoma of duodenum.
Frangenheim	(50)	Squamous-celled carcinoma of gum, mucoid carcinoma of ileum.

Götting	(56)	Squamous-celled carcinoma of larynx, adenocarcinoma of rectum, medullary carcinoma of stomach.
Hansemann	(65)	Carcinoma of esophagus, carcinoma of stomach.
"		Carcinoma of tongue, carcinoma of esophagus.
Hauser	(67)	Adenocarcinoma of rectum, medullary carcinoma of stomach.
Hofbauer	(73)	Papillary carcinoma of Fallopian tube, squamous-celled carcinoma of cervix.
Israël	(75)	Carcinoma of tongue, carcinoma of jejunum.
Kaufmann	(79)	Carcinoma of breast, carcinoma of ovary.
Keding	(81)	Carcinoma of esophagus, carcinoma of stomach.
Klebs	(84)	Carcinoma of left breast, carcinoma of left ovary.
Lannois	(98)	Carcinoma of stomach, carcinoma of duodenum.
Mandry	(107)	Carcinoma of thigh, carcinoma of leg.
"		Carcinoma of breast, carcinoma of ovaries.
Michelsohn	(112)	Carcinoma of breast, carcinoma of uterus, adenocystoma of ovary.
Nehrkorn	(117)	Carcinoma of breast, carcinoma of uterus.
Ogata	(121)	Carcinoma of esophagus, carcinoma of stomach.
Pignal	(131)	Carcinoma of esophagus, carcinoma of stomach.
Pirscher	(130)	Carcinoma of uterus, carcinoma of ovary.
Ravenna	(136)	Carcinoma of esophagus, carcinoma of colon.
Reutter	(140)	Carcinoma of esophagus, carcinoma of stomach.
Richter	(143)	Carcinoma of breast, carcinoma of uterus.
"		Carcinoma of ovary, carcinoma of intestine.
Rosenbach	(145)	Squamous-celled carcinoma of esophagus, adenocarcinoma of pylorus.
v. Scheel	(153)	Carcinoma of stomach, carcinoma of liver.
Simon	(163)	Carcinoma of bladder, carcinoma of kidney pelvis.
Sumpter	(168)	Carcinoma of right ear, carcinoma of left ear.
Taylor	(171)	Adenocarcinoma of uterus, carcinoma of both ovaries.
Walter	(184)	Carcinoma of breast, carcinoma of uterus, adenocystoma of ovary.
Warthin	(187)	Adenocarcinoma of intestine, adenocarcinoma of gall-bladder.
Winiwarter	(194)	Carcinoma of right side of tongue, carcinoma of left side of mouth.
Wehmer	(188)	Carcinoma of body of uterus, adenocarcinoma of ovary.
Wooley	(195)	Mesotheliomata of both adrenals.

MULTIPLE CARCINOMATA IN VARIOUS ORGANS

Altschul	(5)	Carcinoma of lower lip, carcinoma of hands, colloid carcinoma of cecum.
"		Squamous-celled carcinoma of bladder, adenocarcinoma of stomach.
Beck	(13)	Epithelioma of uterus, cancer of colon.
Becker	(14)	Carcinoma of eyelid, carcinoma of ear.
Besche	(17)	Carcinoma of lip, carcinoma of penis.
"		Carcinoma of face, carcinoma of stomach.
"		Carcinoma of lip, carcinoma of rectum.
de Beurmann	(18)	Carcinoma of face, carcinoma of pylorus.
Bryant	(26)	Carcinoma of nose, carcinoma of breast.
Chiari	(30)	Carcinoma of colon, carcinoma of vulva.
Chilesotti	(31)	Carcinoma of neck, carcinoma of lumbar region.
Cordes	(33)	Carcinoma of foot, adenocarcinoma of stomach.
Cullen	(34)	Squamous-celled carcinoma of skin, adenocarcinoma of prostate (dog).
Deetz	(36)	Squamous-celled carcinoma of gall-bladder, carcinoma of rectum (cylindrical-celled) dermoid of ovary.
Feilchenfeld	(45)	Carcinoma of stomach, carcinoma of breast.
Fraenkel	(48)	Carcinoma of breast, carcinoma of intestine.
Graviller	(57)	Carcinoma of lip, carcinoma of breast.
Hansemann	(65)	Carcinoma of stomach, carcinoma of bronchi.
"		Carcinoma of stomach, carcinoma of ovary.
Hauser	(67)	Carcinoma of ear, carcinoma of pylorus.
Herschel	(68)	Carcinoma of skin, carcinoma of esophagus.
Herxheimer	(71)	Carcinoma of cheek, carcinoma of liver.
Hutchinson	(74)	Carcinoma of face, carcinoma of breast.
Kaufmann	(79)	Carcinoma of eye, carcinoma of hand.
Klebs	(84)	Carcinoma of eyelid, carcinoma of rectum.
Krönig	(91)	Carcinoma of stomach, carcinoma of uterus.
Kuster	(94)	Carcinoma of nose, carcinoma of breast.
Lubarsch	(104)	Carcinoma of breast, carcinoma of stomach.
"		Carcinoma of uterus, carcinoma of stomach.
Michelsohn	(112)	Carcinoma of nose, carcinoma of breast.
Nehrkorn	(117)	Carcinoma of bladder, carcinoma of anus.
Pusateri	(113)	Adenocarcinoma of breast, carcinoma of stomach.
Richter	(143)	Adenocarcinoma of thyroid, carcinoma of ovary.
Redlich	(138)	Carcinoma of lung, carcinoma of ileum.
"		Carcinoma of colon, carcinoma of ovary.
Reutter	(140)	Carcinoma of stomach, carcinoma of uterus.
Schwarzwaller	(160)	Carcinoma of labia, carcinoma of breast.
Schwedenberg	(161)	Carcinoma of colon, carcinoma of breast.
Tannberg	(170)	Carcinoma of duodenum, carcinoma of bladder.
Tixier	(176)	Carcinoma of larynx, carcinoma of thyroid.
Tsuji	(177)	Carcinoma of nose, carcinoma of uterus.
Turner	(178)	Carcinoma of lip, carcinoma of penis.
Vander Veer	(180)	Carcinoma of breast, epithelioma of skin (of breast).
Venulet	(181)	Adenocarcinoma of thyroid, carcinoma of uterus.
"		Adenocarcinoma of stomach, carcinoma of lip.
"		Adenocarcinoma of stomach, carcinoma of uterus.
Volkmann	(183)	Carcinoma of skin of buttocks, carcinoma of rectum.
Warthin	(187)	Adenocarcinoma of ovary, colloid carcinoma of gall-bladder.
Winiwarter	(194)	Carcinoma of both breasts, carcinoma of jejunum.
"		Carcinoma of lower lip, carcinoma of glabella.
"		Carcinoma of tongue, carcinoma of scar in skin.
"		Carcinoma of nose, carcinoma of stomach.
"		Carcinoma of ear, carcinoma of stomach.
Ziba Shin-Iz	(196)	Carcinoma of esophagus, carcinoma of larynx.
"		Squamous-celled carcinoma of esophagus, adenocarcinoma of trachea.

DIFFERENT TUMORS IN THE SAME ORGAN

Albrecht	(4)	Carcinoma sarcomatodes of uterus.
Ballin	(7)	Carcinoma sarcomatodes of uterus.
Becker	(14)	Melanotic sarcoma and carcinoma of the face.
Behrendsen	(16)	Cholesteatoma of pons, glioma of left cerebral hemisphere.

Benthin	(15)	Carcinoma sarcomatodes of uterus.
Coenen	(32)	Carcinoma and sarcoma of breast.
Dorsch	(38)	Carcinoma and sarcoma of breast.
Emanuel	(43)	Carcinoma and sarcoma of uterus.
Forster	(46)	Carcinoma and sarcoma of thyroid.
Fraenkel	(48)	Carcinoma sarcomatodes of uterus.
Frangenheim	(50)	Carcinoma and sarcoma of esophagus.
v. Franqué	(51)	Adenocarcinoma of cervix and round-celled sarcoma of body of the uterus.
Gebhard	(52)	Carcinoma and sarcoma of uterus.
Glinski	(55)	Adenocarcinoma and sarcoma of uterus.
Haenel	(62)	Sarcoma and neuroganglioma of brain.
Hansemann	(65)	Carcinoma sarcomatodes of gall-bladder.
Herxheimer	(70)	Carcinoma sarcomatodes of esophagus.
Iwanoff	(76)	Carcinoma and sarcoma of uterus.
Kahler	(77)	Carcinoma sarcomatodes of pharynx.
Kaufmann, E.	(78)	Carcinoma sarcomatodes of breast.
"		Chondro-carcino-sarcoma of breast.
Kaufmann, C.	(80)	Carcinoma and sarcoma of thyroid.
Kettle	(82)	Carcinoma and sarcoma of breast.
Klein	(85)	Carcinoma and sarcoma of uterus.
Klein, H.	(86)	Carcinoma sarcomatodes of nasal sinuses.
Kocher	(87)	Adenocarcinoma, spindle- and giant-celled sarcoma of thyroid.
Krompecher	(90)	Carcinoma and sarcoma of bladder.
"		Carcinoma and sarcoma of mouth.
"		Carcinoma and sarcoma of breast.
Kubinyi	(92)	Carcinoma and sarcoma of uterus.
Kummer	(93)	Carcinoma and sarcoma of thyroid.
Landsteiner	(96)	Carcinoma and sarcoma of gall-bladder.
Lindemann	(101)	Carcinoma sarcomatodes of stomach.
"		Carcinoma sarcomatodes of uterus.
Lippmann	(102)	Carcinoma sarcomatodes of ovary.
Loeb	(103)	Carcinoma and sarcoma of thyroid (white rat).
Maier	(106)	Carcinoma and sarcoma of tibia.
Meyer	(111)	Carcinoma and sarcoma of uterus.
Michelson	(113)	Carcinoma sarcomatodes of pancreas.
Nebesky	(116)	Carcinoma and sarcoma of uterus.
Niebergall	(118)	Carcinoma, sarcoma and polyp of uterus.
Opitz	(122)	Carcinoma sarcomatodes of uterus.
Orth	(124)	Carcinoma and sarcoma of breast.
Quekenstedt	(134)	Carcinoma sarcomatodes of stomach.
Rabl-Rückhardt	(135)	Carcinoma and sarcoma of ovary.
Rezek	(141)	Glioma of substantia nigra, sarcoma of right temporal lobe.
Ritter	(144)	Carcinoma and sarcoma of uterus.
Rosenstein	(146)	Carcinoma sarcomatodes of uterus.
Rothacker	(147)	Carcinoma and sarcoma of ovary.
Saltykow	(149)	Carcinoma and spindle-celled sarcoma of thyroid.
"	(150)	Carcinoma sarcomatodes of uterus.
"	(150)	Carcinoma and sarcoma of liver.
"	(150)	Carcinoma and sarcoma of lung.
Shaller	(151)	Adenocarcinoma and giant-celled sarcoma of uterus.
Schlagenhaufer	(156)	Carcinoma and giant-celled sarcoma of breast.
Schmorl	(158)	Carcinoma and sarcoma of thyroid.
Schone	(159)	Carcinoma and sarcoma of thyroid (dog).
Stein	(166)	Carcinoma sarcomatodes of uterus.
Stromeyer	(167)	Cholesteatoma and sarcoma of temporal lobe of brain.
Takano	(169)	Carcinoma sarcomatodes of breast.
Taylor	(171)	Carcinoma and sarcoma of thyroid.
"		Adenocarcinoma and sarcoma of uterus.
"		Adenocarcinoma and sarcoma of body of uterus, epithelioma of cervix.
Wehmer	(188)	Carcinoma and sarcoma of breast.
Wells	(190)	Alveolar carcinoma, angiosarcoma of thyroid (dog).

DIFFERENT TUMORS IN SAME SYSTEM OF ORGANS

Beadles	(10)	Carcinoma of uterus, sarcoma of breast.
Czerny	(35)	Carcinoma of one breast, sarcoma of the other breast.
Haberer	(61)	Carcinoma of tongue, spindle-celled sarcoma of epiglottis.
Langdon	(97)	Fibrocystoma of pons, fibropsammoma of dura.
Scheel	(152)	Carcinoma of breast, spindle-celled sarcoma of ovary.
Schiller	(155)	Carcinoma of tongue, sarcoma of epiglottis.
Thierfelder	(175)	Squamous-celled carcinoma of esophagus, spindle-celled sarcoma of stomach.
Vander Veer	(180)	Carcinoma of breast, multilocular ovarian cyst.
Walter	(185)	Carcinoma of esophagus, spindle-celled sarcoma of stomach.

DIFFERENT TYPES OF TUMORS IN VARIOUS ORGANS

Auerbach	(6)	Carcinoma of gall-bladder, spindle-celled sarcoma of leg.
Bartel	(8)	Neuromata at base of brain, endothelioma of dura mater.
Bartlett	(9)	Carcinoma of thyroid, adrenal mesothelioma, congenital cystic kidneys, hemangioma of liver (dog).
"		Adenocarcinoma of thyroid, mixed tumor of breast, adenoma of adrenal (dog).
Beadles	(10)	Epithelioma of pharynx, malignant adenoma of kidney.
"		Carcinoma of breast, sarcoma of skin of groin.
Beck	(12)	Carcinoma of gall-bladder, spindle-celled sarcoma of thyroid.
Bevacque	(19)	Peritheliomata of bone, lymphosarcoma of lymph glands.
Blackburn	(20)	Sarcoma of dura, carcinoma of stomach, round-celled of testicle.
Borst	(25)	Carcinoma of thyroid, fibroma of kidney, fibroma of uterus, papilloma of skin.
Cathcart	(28)	Melanotic sarcoma, scirrhous carcinoma.
Chambers	(29)	Carcinoma of both breasts, sarcoma of uterus, sarcoma of skin.
Coenen	(32)	Sarcoma of fascia, myoma of esophagus, hypophysis tumor.
Foster	(47)	Hypernephroma of kidney, scirrhous carcinoma of stomach.
"		Hypernephroma of kidney, carcinoma of stomach.
Frangenheim	(50)	Endothelioma of dura, carcinoma of ovary.
Grawitz	(58)	Carcinoma of small intestine, sarcoma of broad ligament, myoma of uterus.
Griffin	(59)	Carcinoma of esophagus, sarcoma of skin.
Grunfeld	(60)	Colloid carcinoma of stomach, angioendothelioma of stomach.
Hanot	(63)	Carcinoma of liver, sarcoma of uterus.
Hansemann	(64)	Glioma cerebri, myxoma of stomach, sarcoma of liver.

Herxheimer	(69)	Carcinoma of stomach, sarcoma of brain, myoma of uterus, polyp of stomach.
Krakiewicz	(88)	Squamous-celled carcinoma of esophagus, lymphosarcoma of mediastinum.
Kretz	(89)	Carcinoma of esophagus, endothelioma of dura.
Landau	(95)	Osteoma of jaw, adenocarcinoma of intestine and rectum, fibrosarcoma of breast.
van Leuwen	(99)	Basal-celled carcinoma of skin, mixed tumor of parotid.
Lewis	(100)	Angioma of liver, angioma of kidney, adenoma of liver, adenoma of adrenal, polyp of uterus, myoma of uterus, malignant myoma of broad ligament, fibroma of ovary, pigmented nævi.
Mann	(108)	Epithelioma of penis, endothelioma of dura.
Markus	(109)	Carcinoma of liver and gall-bladder, melanotic sarcoma of ovaries.
Nehrkorn	(117)	Carcinoma of uterus, melanotic sarcoma of rectum.
Nothdurft	(119)	Carcinoma of both kidneys, hemangioma of breast.
Phillipson	(129)	Carcinoma of gall-bladder, sarcoma of skin.
Scheven	(154)	Carcinoma of stomach, mixed tumor of kidney, psammoma of left striate body.
Schmincke	(157)	Carcinoma of gall-bladder, sarcoma of uterus.
Simon	(162)	Carcinoma of liver, melanotic sarcoma of eye.
Sliwinsky	(164)	Carcinoma of breast, carcinoma of stomach, papillary adenoma of kidney, lipoma of mesentery, endothelioma of dura, multiple adenomata of thyroid, carcinoma of liver.
Taylor	(171)	Carcinoma of thyroid, sarcoma of mediastinum.
"		Carcinoma of liver, melanotic sarcoma of choroid.
Thalmessinger	(172)	Cystoma of ovary, sarcoma of peritoneum.
"		Carcinoma of penis, lymphosarcoma of inguinal lymph gland.
"		Adenoma of breast, osteosarcoma of tibia.
"		Carcinoma of right ear and cheek, large round-celled sarcoma of neck.
Ugdalena	(179)	Adenoma of hypophysis, carcinoma of uterus.
Vander Veer	(180)	Carcinoma of breast, sarcoma of dura.
Walter	(184)	Carcinoma of pancreas, sarcoma of liver.
"	(185)	Carcinoma of stomach, psammoma of brain, liposarcoma of kidney.
Wehmer	(188)	Carcinoma of uterus, adenocarcinoma of ovary, sarcoma of peritoneal cavity.
Wooley	(195)	Gliosarcoma of brain, endothelioma of pleura, endothelioma of Glisson's capsule.

BIBLIOGRAPHY

1. Abel, Karl: Ein Fall von circumscripten Cervixcarcinom und gleichzeitigen isolierten Krebsknoten im Fundus. Berl. klin. Wchnschr., 1889, XXVI,675.

2. Abesser: Quoted by Hansemann (65).

3. Adami, J. G.: Concerning the Causation of Cancerous and Other New Growths. Yale M. J., 1901, VII, 309.

4. Albrecht, H.: Ueber das Karzinosarkom des Uterus. Frankf. Ztschr. f. Path., 1908, II, 191.

5. Altschul: Med. Klin., 1912, IX, 354; quoted by Theilhaber and Edelberg (173).

6. Auerbach, F.: Ueber Multiplizität primärer maligner Tumoren. Inaugural Dissertation, Heidelberg, 1911.

7. Ballin, Arnold: Ueber einen Fall von Karcinomsarkom der Uterusschleimhaut. Inaugural Dissertation, Leipzig, 1903.

8. Bartel, Julius: Ausgedehnte multiple primäre Tumorbildung der Meningen des Gehirnes und des Rückenmarkes mit multipler Neurofibrombildung. Centralbl. f. allg. Path. u. path. Anat., 1905, XVI, 742.

9. Bartlett, Frank K.: Multiple Primary Malignant Tumors. Arch. Int. Med., 1914, XIII, 624.

10. Beadles, Cecil F.: Cases of Two Primary Malignant Neoplasms in the Same Individual. Tr. Path. Soc. Lond., 1897, XLVII, 236.

11. *Idem.*: Esophagus with Two Malignant Growths. Tr. Path. Soc. Lond., 1897, XLVII, 68.

12. Beck, Karl: Ueber Multiplicität primärer maligner Tumoren, zugleich ein Beitrag zur Metaplasiefrage. Arch. f. path. Anat., 1909, CXCVI, 335.

13. Beck: Prag. klin. Wchschr., 1883; quoted by Wooley (195).

14. Becker: Zur Kasuistik multipler primärer Tumoren. Beitr. z. klin. Chir., 1895, XIV, 146.

15. Benthin, W.: Zur Kenntnis des Carcinoma Sarcomatodes des Uterus. Beitr. z. path. Anat. u. z. allg. Path., 1915, LX, 163.

16. Behrendsen: Ein Fall von gleichzeitigem Auftreten zweier verschiedenartigen Hirntumoren. Deutsche med. Wchnschr., 1899, XXV, 710.

17. de Besche, A.: Multiple kancere. Norsk. Mag. f. Laegeividensk, 1908, 5R., V., 533.

18. de Beurmann: Un cas de tumeurs primitives multiples chez le même sujet. Bull de L'Ass. franç. p. l'étude du cancer, 1911, IV, 116.

19. Bevacqua, Alfredo: Ueber multiple Knochen-Peritheliome mit Lymphosarkon der Lymphdrüsen. Arch. f. path. Anat., 1910, CC, 101.

20. Blackburn: Path Suppl. 39. Annual Rep. Gov. Hosp. f. Insane U. S. A. 1894: quoted by Vander Veer (180).

21. Blaschko, H.: Eine Seltene erbliche Lipombildung. Arch. f. path. Anat., 1891, CXXIV, 175.

22. Bockel: Prog. de chir. 1888; quoted by Theilhaber and Edelberg (173).

23. Borchardt: Quoted by Krakiewicz (88).

24. Borrmann, Robert: Die Beurteilung multipler karcinome im Digestionstraktus. Beitr. z. path. Anat. u. allg. Path., 1910, XLVIII, 576.

25. Borst, M.: Die Lehre von den Geschwülsten. Wiesbaden, 1902, Bd. I, 58.

26. Bryant J. D.: Diseases of the Breast. 1884.

27. Bucher, Robert: Beiträge zur Lehre vom Carcinom. Beitr. z. path. Anat. u. z. allg. Path., 1893, XIV, 71.

28. Cathcart: Edinburgh Medico-Chir Soc., Dec. 2, 1896; quoted by Vander Veer (180).

29. Chambers, Porter F.: Multiple Neoplasma. Am. J. Obst., 1913, LXVIII, 557.

30. Chiari: Ber. d. k. k. Krankenanst. Rudolph Stiftung in Wien, 1881.

31. Chilesotti, E.: Les carcinomes calcifiés de la peau, étude sur un carcinoma de la peau, primitif, multiple, calcifié. Rev. méd. de la Suisse Rom., 1904, XXIV, 317.

32. Coenen, H.: Ueber Mutationsgeschwülste und ihre Stellung im Onkologischen System. Beitr. z. klin. Chir., 1910, LXVIII, 605.

33. Cordes, H.; Ein casuistischer Beitrag zur Multiplizität der primären Carcinome. Arch. f. path. Anat., 1896, CXLV, 422.

34. Cullen, E. K.: A Case of Multiple Tumors in a Dog. Bull. Johns Hopkins Hosp., 1907, XVIII, 101.

35. Czerny: Quoted by Nehrkorn (117).

36. Deetz, Eduard: Vier weitere Fälle von Plattenepithel-Krebs der Gallenblase. Arch. f. path. Anat., 1901, CLXIV, 381.

37. Devis and Gallavardin: Quoted by Krakiewicz (88).

38. Dorsh: Ueber Carcinom und Sarkom derselben Mamma. Inaugural Dissertation, Würzburg, 1896.

39. Eckardt, K.: Zur Casuistik mehrfacher maligner epithelialer Neubildungen am Uterus. Arch. f. Gynaek., 1898, LV, 1.

40. Ehrlich, P., and Apolant: Zur Kenntnis der Sarkomentwickelung bei Carcinomtransplantationen. Centralbl. f. allg. Path. u. path. Anat., 1906, XVII, 513.

41. Eichbaum: Inaugural Dissertation, Greifswald, 1904.

42. Elischer: Quoted by Hansemann (65).

43. Emanuel, R.: Ueber gleichzeitiges Vorkommen von Carcinom und Sarkom im Uteruskörper. Ztschr. f. Geburtsh. u. Gynaek., 1896, XXXIV, 1.

44. d'Erchia, Florenzo: Beitrag zum Studium des primären Uteruskrebses. Ztschr. f. Geburtsh. u. Gynaek., 1899, XXXVIII, 417.

45. Feilchenfeld: Inaugural Dissertation, Berl., 1904; quoted by Theilhaber and Edelberg (173).

46. Förster: Ueber die Geschwülste der Schilddrüse. Würzb. med. Ztschr., 1860; Quoted by Schone (159).

47. Foster, Geo. B. Jr., and Gerhard, C. H.: Two Instances of the Simultaneous Occurrence of Hypernephroma and Carcinoma. New York M. J., 1909, LXXXIX, 154.

48. Fraenkel: Carcino-Sarcoma Uteri. Monatschr. f. Geburtsh. u. Gynaek., 1901, XIV, 684.

49. Fraenkel: Quoted by Theilhaber and Edelberg (173).

50. Frangenheim, Paul: Multiple Primartumoren. Arch. f. path. Anat., 1906, CLXXXIV, 201.

51. v. Franqué: Ueber Sarcoma Uteri. Ztschr. f. Geburtsh. u. Gynaek., 1899, XI, 183.

52. Gebhard: Quoted by Herxheimer (70).

53. Gellhorn, George: Zur Casuistik der Hornkrebse des Gebärmutterkörpers. Ztschr. f. Geburtsh. u. Gynaek., 1897, XXXVI, 430.

54. Genersich, Anton: Multiple Neurome. Arch. f. path. Anat., 1870, XLIX, 15.

55. Glinski: Quoted by Krakiewicz (88).

56. Gotting, G.: Zur Multiplicität primärer Carcinome. Ztschr. f. Krebsforsch., 1909, VII, 675.

57. Graviller: Canada M. J., 1873, II; quoted by Theilhaber and Edelberg (173).

58. Grawitz, P.: Ueber multiple Primärtumoren. Deutsche med. Wchnschr., 1904, XXX, 1794.

59. Griffin and Dartigues: Bull. Soc. anat. de Paris, 1898, LXXIII, 570.

60. Grünfeld, R. L.: Zur Duplicität maligner protopatischer Tumoren. München. Med. Wchnschr. 1901, XLVIII, II, 1279.

61. Haberer, H.: Sarkom und Carcinom bei demselben Individuum. Arch. f. klin. Chir. 1904, LXXIII, 609.

62. Haenel: Quoted by Stromeyer (167).

63. Hanot: Bull. Soc. anat. de Par. 1884, LIX, 72; quoted by Thalmessinger (172).

64. Hansemann: Ueber das gleichzeitige Vorkommen mehrerer primärer Geschwülste bei einem Individuum. Deutsche Med. Wchnschr., 1904, XXX, 119.

65. *Idem*: Das gleichzeitige Vorkommen verschiedenartiger Geschwülste bei derselben Person. Ztschr. f. Krebsforsch., 1904, I, 183.

66. Hauser: Quoted by Walter (184).

67. Hauser, G.: Giebt es eine primäre zur Geschwulstbildung führende Epithelerkrankung? Beitr. z. path. Anat. u. z. allg. Path., 1903, XXXIII, 1.

68. Herschel, Karl: Zur Multiplicität maligner Neubildungen, speciell der Carcinome. Inaugural Dissertation, Halle, 1895.

69. Herxheimer, G., and Reinke, F.: Pathologie des Krebses. Ergebn. d. allg. Path. u. path. Anat., 1912, XVI, II, 280.

70. Herxheimer, G.: Das Carcinoma sarcomatodes. Beitr. z. path. Anat., 1908, XLIV, 150.

71. Herzheimer, G.: Kasuistische Mitteilung zur Geschwülstlehre. Centralbl. f. allg. Path. u. path. Anat., 1908, XIX, 703.

72. Herzog, Georg.: Zwei primäre Karzinome auf dem Boden alter tuberkulöser Darmgeschwüre. Beitr. z. path. Anat. u. allg. Path., 1913, LV, 177.

73. Hofbauer: Ueber primäres Tubencarcinom. Arch. f. Gynaek., 1898, LV, 316.

74. Hutchinson, J.: On Cancer and the cancerous Process. Arch. Surg., 1892, III, 335.

75. Israel, O.: Ueber ein Fall von gleichzeitigem Auftreten zweier primärer Carcinome. Berl. klin. Wchnschr., 1883, XX, 683.

76. Iwanoff, N. S.: Drüsiges cystenhaltiges Uterusfibromyom kompliciert durch Sarkom und Carcinom. Monatsch. f. Geburtsh. u. Gynaek., 1898, VII, 295.

77. Kahler, O.: Ein Carcino-Sarkom des Recessus piriformis bei Ekchondrose des Ringknorpels. Deutsche med. Wchnschr., 1906, XXIV, 644.

78. Kaufmann, Ed.: Lehrbuch d. speziellen pathologische Anatomie. Berlin, 1909, V. ED., p. 1053.

79. Kaufmann, C.: Ueber Multiplicität des primären Carcinoms. Arch. f. path. Anat., 1879, LXXV, 317.

80. Kaufmann, C.: Die Struma maligna. Primäres Sarkoma und Carcinoma strumae. Deutsche Ztschr. f. Chir., 1879, XI, 401.

81. Keding: Die Parasitentheorie der Geschwülstentstehung im Vergleich zu den tatsächlichen Erfahrungen über multiple Tumoren. Inaugural Dissertation, Greifswald, 1903.

82. Kettle, E. H.: Carcinoma and Sarcoma of the Same Breast. Lancet, 1912, II, 750.

83. Kidner, F. C.: Sarcoma and Carcinoma in the Same Patient. Boston M. & S. J., 1908, CLVIII, 836.

84. Klebs: Handbuch der path. Anatomie, Bd. I, p. 190.

85. Klein, G.: Uterus-Sarkom. München. med. Wchnschr., 1890, XXXVII, 170.

86. Klein, H.: Pathologisch-histologische Studie über eine seltene Combination von Sarkom und Carcinom der Nasenhöhle. Inaugural Dissertation, Würzburg, 1898.

87. Kocher, Theodor.: Ueber glykogenhaltige Strumen. Arch. f. path. Anat., 1899, CLV, 532.

88. Krakiewicz, Anton: Zur Kasuistik multipler primärer (Multiplicitas diversi generis) maligner Geschwülste. Wien. klin. Wchnschr., 1913, XXVI, 1204.

89. Kretz, R.: Zwei maligne Neubildungen in einem Individuum mit Metastasen beider in einem Organ. Wien. klin. Wchnschr., 1893, VI, 196.

90. Krompecher, E.: Ueber die Beziehungen zwischen Epithel und Bindegewebe. Beitr. z. path. Anat. und allg. Path., 1908, XLIV, 88.

91. Krönig: Gleichzeitiges Vorkommen des Karzinoms im Uterus und Magen. München med. Wchnschr., 1902, XLIX, II, 1444.

92. v. Kubinyi, Paul: Beiträge zur Frage der sarkomatösen Entartung der Gebärmuttermyome. Arch. f. Gynaek., 1912, XCVII, 237.

93. Kummer, E.: Sarco-adénome du corps thyroïde ayant simulé une strumite simple. Rev. méd. de la Suisse Rom., 1898, XVIII, 702.

94. Kuster: Quoted by Walter (184).

95. Landau, H.: Krebs und Sarkom am gleichen Menschen. München. med. Wchnschr., 1905, LII, I, 650.

96. Landsteiner, K.: Plattenepithelkarzinom und Sarkom der Gallenblase in einem Fall von Cholelithiasis. Ztschr. f. klin. Med., 1907, LXII, 427.

97. Langdon, F. W.: Multiple Tumors of the Brain. Brain, 1895, XVIII, 551.

98. Lannois et Courmont: Coexistence de cancer du cardia et de cancer du duodenum. Mém. et compt-rend. Soc. de sc. méd. de Lyon, 1894, XXXIII, pt. 2, 197.

99. van Leuwen, Th. M.: Multiple Epitheliome der Haut mit Mischgeschwulst der Parotis. Arch. f. path. Anat., 1912, CCVII, 330.

100. Lewis, Paul A.: Multiple Primary Heterogeneous Tumors. Centralbl. f. allg. Path. u. path. Anat., 1907, XVIII, 485.

101. Lindemann, A.: Ein Beitrag zum Carcinoma sarcomatodes. Ztschr. f. Krebsforsch., 1907-08, VI, 419.

102. Lippmann, H.: Ueber einen Fall von Carcinoma sarcomatodes mit gemischten und reinen Sarcommetastasen. Ztschr. f. Krebsforsch., 1905, III, 293.

103. Loeb, L.: Mixed Tumors of the Thyroid Gland. Am. J. M. Sc., 1903, CXXV, 243.

104. Lubarsch, O.: Pathologie des Karzinoms. Ergebn. d. allg. Path. und path. Anat. 1904-05, X, 924.

105. Lyon, I. P.: Adiposis and Lipomatosis Considered in Reference to Their Constitutional Relations and Symptomatology. Arch. Int. Med., 1910, VI, 28.

106. Maier, Rudolf: Bemerkungen über sarcomatöse und krebsige Degeneration. Arch. f. path. Anat., 1877, LXX, 398.

107. Mandry, G.: Ueber symmetrische primäre Carcinome. Beitr. z. klin. Chir., 1891-2, VIII, 589.

108. Mann and Stranahan: Bull. State Hosp. Utica N. Y., 1897, II, 165; quoted by Wells (190).

109. Markus, N.: Gleichzeitige Entwickelung eines Melanosarcoma ovarii und Carcinoma hepatis in der Schwangerschaft. Arch. f. Gyn., 1910, XCII, 659.

110. Meerbeck, Ferdinand: Ueber Multiple Lipome. Inaugural Dissertation, Würzburg, 1837.

111. Meyer, Robert: Veit's Handbuch der Gynækologie, II Aufl., 1908, Bd. III, p. 443.

112. Michelsohn, Julius: Zur Multiplicität der primären Carcinome. Inaugural Dissertation, Berlin, 1889.

113. Michelson, H.: Ein Fall primären Sarkocarcinom des Pancreas. Inaugural Dissertation, Würzburg, 1894.

114. Monkeberg: Quoted by Hansemann (65).

115 de Morgan and Coupland, S.: Case of Multiple Neuroma of the Forearm. Trans. Path. Soc. Lond., 1875, XXVI, 2.

116. Nebesky, O.: Ueber das gleichzeitige Vorkommen von Sarkom und Carcinom im Uterus. Arch. f. Gynaek., 1904, LXXIII, 653.

117. Nehrkorn: Multiplicität primärer maligner Tumoren. München. med. Wchnschr., 1901, XLVIII, 581.

118. Niebergall: Sarkom, Carcinom, Myom und Schleimpolypen an ein und demselben Uterus. Arch. f. Gynaek., 1896, L, 129.

119. Nothdurft: Ein von mehrfachen Tumorbildung. Prag. med. Wchnschr., 1911, XXXVI, 610.

120. Oberndorfer, S.: Ueber Multiplicität von Tumoren. München. med. Wchnschr., 1905, LII, II, 1477.

121. Ogata: Quoted by Theilhaber and Edelberg (173).

122. Opitz, E.: Zwei ungewöhnliche Uteruscarcinome nebst Bemerkungen zur Theorie der bösartigen Geschwülste. Ztschr. f. Geburtsh. u. Gynaek., 1903, XLIX, 169.

123. Orth: Quoted by Landau (95).

124. *Idem*: Quoted by Takano (169).

125. Payne: Vascular Tumors of the Liver, Suprarenal capsules and Other Organs. Trans. Path. Soc. Lond., 1869, XX, 203.

126. Petersen, Walther: Beiträge zur Lehre vom Carcinom. Beitr. z. klin. Chir., 1902, XXXIV, 682.

127. Petersen and Colmers, F.: Anatomische und klinische Untersuchungen über die Magen- und Darmcarcinome. Beitr. z. klin. Chir., 1904, XLIII, 1.

128. Petren, Karl: Ein Fall von multiplen symmetrischen hereditären Lipomen. Arch. f. path. Anat., 1897, CXLVII, 560.

129. Phillipson: Quoted by Wells (190).

130. Pirscher: Quoted by Theilhaber and Edelberg (173).

131. Pignal: Thèse de Lyon 1907; quoted by Theilhaber and Edelberg (173).

132. Polano, Oscar: Ueber Pseudoendotheliome des Eierstocks. Ztschr. f. Geburtsh. u. Gynaek., 1904, LI, I.

133. Pusateri, S.: Beitrag zum Studium der multiplen primären Karzinome. Arch. f. path. Anat., 1911, CCIV, 85.

134. Quekenstedt: Ueber Karzinosarkom. Inaugural Dissertation, Leipzig, 1904.

135. Rabl-Ruckhardt: Beitr. z. Geburtsh. und Gynaek., 1872, I, 76; quoted by Wells (190).

136. Ravenna: Quoted by Theilhaber and Edelberg (173).

137. Recklinghausen (v.): Ueber die multiplen Fibrome der Haut und ihre Beziehungen zu den multiplen Neuromen. Berlin, 1882.

138. Redlich, W.: Statistik des Carcinoms am Berliner Städtischen Krankenhaus am Urban nebst kasuistische Beiträgen. Ztschr. f. Krebsforsch., 1907, v, 261.

139. Reichmann: Quoted by Redlich (138).

140. Reutter, G.: Quelques cas rares de carcinomes. Dissertation Inaug., Lausanne, 1901.

141. Rezek: Quoted by Stromeyer (167).

142. Ribbert: Quoted by Theilhaber and Edelberg (173).

143. Richter, J.: Zur Kasuistik der multiplen primären carcinome. Wien. klin. Wchnschr., 1905, XVII, 865.

144. Ritter, H.: Ueber das gleichzeitige Vorkommen von Carcinom und Sarkom im Uterus. Inaugural Dissertation, Zürich, 1902.

145. Rosenbach: Kasuistischer Beitrag zur Multiplicität primärer Karzinome. Arch. f. path. Anat., 1905, CLXXIX, 567.

146. Rosenstein, S.: Carcinosarcome Uteri bei einem Kinde von zwei Jahren. Arch. f. path. Anat., 1883, XCII. 1911.

147. Rothacker, A.: Zur Frage der Carcinosarkome. Ztschr. f. Krebsforsch, 1913, XII, 39.

148. Russell, B. R. G.: Sarcoma Development Occurring During the Propagation of a Hemorrhagic Adenocarcinoma of the Mamma of the Mouse. J. Path. and Bacteriol., 1809-10, XIV, 344.

149. Saltykow, S.: Ueber das gleichzeitige Vorkommen des Sarkoms und Carcinoms in der Schilddrüse. Centralbl. f. allg. Path. u. path. Anat., 1905, XVI, 547.

150. Saltykow, S.: Beiträge zur Kenntnis des Carcinosarkoms. Centralbl. f. allg. Path. u. path. Anat., 1914, XXV, 419.

151. Schaller, L. F.: Gleichzeitiges Vorkommen von Adenocarcinom und Riesenzellensarkom im multiplen-myomatösen Corpus Uteri. Deutsche med. Wchnschr., 1906, XXXII, 959.

152. Scheel: Hosp. Tid., 4 R., 1896, VII, 855; quoted by Wells (190).

153. Scheel, V.: Aarsberetning. I, 1904, fra Kommunehospitalets Sektionstue Bibliot. f. Laeger., 1905, 8 R., VI, 390.

154. Scheven: Quoted by Walter (184).

155. Schiller, A.: Ueber zwei Fälle von primärem malignem Tumor der Epiglottis. Berl. klin. Wchschr., 1898, XXXV, 906.

156. Schlagenhaufer: Carcinom und Riesenzellsarkom derselben Mamma. Centralbl. f. allg. Path. u. path. Anat., 1906, XVII, 385.

157. Schmincke, A.: Zur Kasuistik primärer Multiplicität maligner Tumoren. Arch. f. path. Anat., 1906, CLXXXIII, 160.

158. Schmorl: Reported by Apolant (H). Die epithelialen Geschwültste der Maus. Arb. a. d. k. Inst. f. exper. Therap. zu Frankf. a. M., 1906, Hft. 1, 7.

159. Schöne, Georg: Sarkom und Karzinom in einer Schilddrüse beim Hunde. Arch. f. path. Anat., 1909, CXCV, 169.

160. Schwarzwaller: Report. Berl. klin. Wchnschr., 1902, XXXIX, 444.

161. Schwedenberg, T.: Ueber die Karzinose des Ductus thoracicus. Arch. f. path. Anat., 1905, CLXXXI, 295.

162. Simon: Bull. Soc. anat. de Paris, 1900, XXIV, 213.

163. Simon: Quoted by Theilhaber and Edelberg (173).

164. Sliwinsky, F.: Zur Kasuistik multipler primärer Tumorbildung. Wien. klin. Wchnschr., 1909, XXII, 1134.

165. Slye, Maud: The Incidence of Heritability of Spontaneous Cancer in Mice. J. Med. Research, XXVII, 159.

166. Stein, A.: Carcinomsarcoma Uteri mit Metaplasie des Zylir th zellencarcinoms in Plattenepithelcarcinom. Monatschr. f. Geburtsh. u. Gynaek., 1912, XXXVI, 417.

167. Stromeyer, Fritz: Ueber ein mit Sarkom Kombiniertes Cholesteatom des Gehirnes. Beitr. z. path. Anat. u. allg. Path., 1910, XLVII, 392.

168. Sumpter, W. J. E.: Epithelioma of Both External Ears. Lancet, 1894, I, 1160.

169. Takano, N.: Ueber das Carcinoma Sarcomatodes der Mamma. Arch. f. klin. Chir., 1914, CIII, 155.

170. Tannberg: Quoted by Theilhaber and Edelberg (173).

171. Taylor, M. L.: A Series of Double Malignant Tumors. J. Path. and Bacteriol., 1909-10, XIV, 205.

172. Thalmessinger, Viktor: Ueber Gleichzeitiges Vorkommen von Carcinom und Sarkom. Inaugural Dissertation, Würzburg, 1888.

173. Theilhaber and Edelberg: Zur Lehre von der Multiplicität der Tumoren insbesondere der Carcinome. Deutsche Ztschr. f. Chir., 1912, CLXX, 457.

174. Theilhaber und Hollinger: Die Beschaffenheit des Mesometrium bei Uteruscarcinomen. Arch. f. Gynaek., 1904, LXXIII, 1.

175. Thierfelder: Quoted by Walter (184).

176. Tixier: Quoted by Krakiewicz (88).

177. Tsuji, T.: Ueber die Multiplicität der Karzinome. Beitr. z. Geburtsh. u. Gynaek., 1909, XIV, 299.

178. Turner, G. R.: Epithelioma of Lip and of Penis. Lancet, 1892, I, 1421.

179. Ugdalena, G.: Zwei von einander unabhängige maligne Blastome in demselben Körper. Ztschr. f. Krebsforsch., 1909, VIII, 319.

180. Vander Veer, A.: Report of a series of Cases of Malignant Growths. Surg. Gyn. Obst., 1906, III, 242.

181. Venulet, F. F.: Ueber multiple Geschwülste. Centralbl. f. allg. Path. u. path. Anat., 1914, XXV, 27.

182. Virchow: Die Krankhaften Geschwülsten.

183. Volkmann: Beitr z. klin, Chir 1875.

184. Walter: Inaugural Dissertation, Berlin, 1896.

185. Walter, M.: Ueber das multiple Auftreten primärer bösartiger Neoplasmen. Arch. f. klin. Chir., 1896, LIII, 1.

186. Warstat, G.: Ueber seltene Kombinationen von Carcinomen an dem weiblichen Sexualorganen. Ztschr. f. Krebsforsch., 1912, XI, 527.

187. Warthin, A. S.: Multiple Primary Carcinoma. J. Am. M. Ass., 1899, XXXII, 963.

188. Wehmer, F.: Ueber gleichzeitiges Vorkommen bösartiger Geschwülste des Uterus und des Ovarium. Inaugural Dissertation, Würzburg, 1894.

189. Wehner, E.: Beitrag zur Frage der Carcinosarkome unter Mitteilung eines Mamma-tumors. Centralbl. f. allg. Path. u. path. Anat., 1915, XXVI, 77.

190. Wells, H. G.: Mutiple Primary Malignant Tumors. J. Path. and Bacteriol., 1901, VII, 357.

191. Westphalen, H.: Multiple Fibrome der Haut und der Nerven mit Uebergang in Sarkom und mit Metastasenbildung. Arch. f. Path. Anat., 1887, CX, 29.

192. Wiel, Otto: Ueber multiple symmetrische Lipome. Inaugural Dissertation, Würzburg, 1904.

193. Williams, R.: Malignant and Non-Malignant Tumors of Bilateral Origin. Lancet, 1910, I, 426.

194. Winiwarter: Beiträge zur Statistik der Carcinome. Stuttgart, 1878; quoted by Kaufmann (79).

195. Wooley, P. G.: Notes on Multiple Primary Tumors. Boston Med. and Surg. J., 1903, CXLVIII, 1.

196. Ziba Shinlz: Ueber die Combination von Larynx-bezw. Tracheal-carcinom mit Oesophagus carcinom. Arch. f. Laryngol. u. Rhinol., 1911, XXV, 401.

IDIOPATHIC BACILLUS AEROGENES CAPSULATUS INFECTION

By HORACE GREELEY, M. D., Brooklyn, N. Y.

Since Welch and Nuttall [1] published a description of this organism, in 1892, many reports of infection with it have appeared in the literature. Although most of the cases recorded have been instances where crushing or severe mechanical injury was followed by a phlegmonous and usually fatal inflammation, for which the bacillus in question was adjudged to be responsible, some of the patients have had no such predisposing injury. The puerperal cases, of course, may be said to follow the severe traumatisms not uncommonly associated with difficult labor, but such cases of this infection as that reported by Gwyn [2], which presented at first clinically as chorea, cannot be attributed to traumatism, at least to external traumatism. In this case, 13 days before death, a blood culture showed the presence of the *B. aërogenes capsulatus* alone. Later, endocarditis was discovered and, in addition to the bacillus in question, streptococci were found in another blood culture.

As the organism is a recognized common inhabitant of the intestinal tract and of distinct pathogenic abilities, it would be expected that lesions of the abdominal organs, due to various pathological conditions such as tumor, obstruction, ulceration, acute indigestion etc., and the inevitable traumatisms of abdominal surgery, would, not infrequently, be followed by inflammations directly caused by this bacillus. As the predisposing conditions in such cases are usually obscure they may properly be classed as idiopathic infections.

A cursory glance at recent literature, however, yields very little to prove such a supposition, perhaps because bacteriological investigations have been so seldom undertaken: Libman [3] reported a case of gall-bladder infection due to this organism. Baugher [4] reported three cases—one in which suppurative perforation of the gall-bladder was apparently caused by this organism; another in which it was found in a fistula which followed an operation for cholecystitis and which led to perforation of the stomach; and a third in which it was the infectious agent in a chronic fistula leading to the gall-bladder region, and in an acute right-side empyema, which followed operations necessitated by an appendiceal abscess.

Several authorities [5] have reported certain small epidemics and individual cases of severe diarrhœa in which it seemed reasonable to conclude that the *B. aërogenes capsulatus* was the causative factor. In this connection Hewes and Kendall made the interesting observation that diarrhœas due to this organism were aggravated by such diet (carbohydrates, especially sugar)

as had been demonstrated to be beneficial in cases where dysentery bacilli were operating; while regimens consisting principally of proteins gave the best results in such cases as might be blamed upon the *B. aërogenes capsulatus*.

A case of primary osteomyelitis at the sacro-iliac joint was reported by Cone[6]. The patient died from the generalizing of the infection and the autopsy disclosed post-mortem gaseous accumulations in the spleen, subcutaneous and other tissues. *B. aërogenes capsulatus* was found in necrotic bone around the primary focus.

A case of long continued ear discharge, followed by acute mastoiditis and lateral sinus thrombosis was reported by Shortlidge.[7] The patient, a man, died.

Cramp[8], in summarizing reports of 187 cases of infection with this bacillus said that 76 resulted from compound fractures; 41 from lacerated wounds; 15 from gun-shot injuries; 3 from bites by animals; 2 from gorings by cattle; 21 were post-operative; 8 followed subcutaneous injections; 6 occurred in gynecological or obstetrical cases; and 6 were non-traumatic and, therefore, of similar origin to the cases called idiopathic in this article. The remaining cases of the 187 were not classified.

Besson * says: "The bacillus perfringens (*B. aërogenes capsulatus*) is exceedingly widespread. Achalme found it in the blood of persons suffering from rheumatism and in the myocardium of two individuals who had died of acute articular rheumatism; Veillon and Zuber in gangrenous suppurations (appendicitis, etc.); Guyon, Albarran, Jungano, in urinary abscesses; Fraenkel in an inflammatory swelling; Guillemot in a case of gaseous gangrene; Jungano in cases of chronic urethritis; Chaillous and Benedetti in ocular infections. It is a normal inhabitant of the alimentary canal of man and many of the lower animals, and it possibly plays a part in the etiology of certain forms of diarrhœa (Tissier, Metchnikoff). It is also present in bodies undergoing decomposition."

In connection with inflammatory processes of the gall-bladder and liver I recently had occasion to do some bacteriological and pathological work which disclosed two interesting cases of infection by *B. aërogenes capsulatus*.

The first patient had been under the care of Dr. Earle H. Mayne of this city, who has very kindly supplied me with clinical data sufficient to give a short account of the case.

Mrs. B., a housewife of 52 years of age, in prosperous circumstances, weight about 160 lbs., previously in good health and with a negative disease history, after having been ailing and, more or less, confined to the house for about three months, called in Dr. Mayne, who found her suffering from a remittent fever, reaching from 100° to 104° F. in the afternoons and subsiding slightly in the mornings. There were no other symptoms except such lassitude and anorexia as would naturally accompany any toxæmia producing such elevation of temperature. Upon physical examination, Dr. Mayne found that the patient's liver reached a point half-way between the lower margin of the ribs and the umbilicus. At his request I made laboratory examinations which gave the following findings:

Blood—

Erythrocytes: 4,400,400 (slight poikilocytosis, otherwise the cells were normal).

Leucocytes: 32,400 (neutrophile, 69 per cent; eosinophile, 7.2 per cent; lymphocytes, 17.8 per cent; large mononuclears, 6 per cent.

No malaria plasmodia were present, and the Widal and Wassermann tests were negative. The feces showed nothing beyond the usual miscellaneous assortment of bacteria, a good deal of mucus, and epithelia from the large intestine.

Blood cultures, taken two weeks before the date of the above tests, were negative; but those taken concomitantly gave, after 48 hours' incubation, a pure growth of what subsequently proved to be the *B. aërogenes capsulatus*.

The patient refused an exploratory laparotomy and Dr. Mayne then proceeded to immunize her son with a vaccine which I made from the organism isolated. After three doses had been given the young man, 500 c. c. of his blood were transfused into his mother; again three injections of vaccine into the donor, a transfusion of 800 c. c. to the patient; and, finally, a third series of three doses of vaccine, and a transfusion of 1000 c. c of blood. No noticeable effect was produced, and nothing else that was done for the patient helped her in any way.

During the next three months the patient gradually grew worse, her liver finally reaching to Poupart's ligament. For the last 10 days of this period she was delirious, dying, evidently from toxæmia, after an illness of six months.

An autopsy was obtained by Dr. Raymond Clark, who had cared for the patient during an absence from town of Dr. Mayne. Dr. Clark informs me that the post-mortem disclosed a generalized carcinoma of the liver, which seemed, possibly, to have arisen in the gall-bladder, which was extensively diseased. No bacteriological examination was made at this time.

Since the high temperature prevailing during the six months illness necessitates an explanation other than the presence of the neoplasm, and as the positive blood cultures and leucocytosis demonstrated the presence of an infection with *B. aërogenes capsulatus* and a systemic reaction thereto, I think it justifiable to conclude that the neoplasm afforded a gateway by which this common saprophyte was enabled to maintain

Number Cases	Nature of Case	Outcome		Positive Culture	Reported by
		Deaths	Recoveries		
1	Puerperal.	1	....	Few days before death.	Young & Rhea, Boston M. & S. J., 1909, CLX, p. 401.
1	Chorea, endocarditis.	1	....	13 days before death.	Gwyn, Bull. J. Hopkins Hosp., 1899, X, p. 134.
4	Severe injury.	4	....	Few hours before death.	Hewitt, J.A.M.A., Apl, 1, 1911, p. 959.
1	Severe injury.	1	....	3 hours before death.	Cole, Bull. J. Hopkins Hosp., 1902, XIII, p. 234.
1	Severe injury.	1	....	1 day before death.	Baugher, J. A. M. A., Apr. 11, 1914, p. 1153.
1	Cholecystitis.	....	1	.....	Baugher, J. A. M. A., Apr. 11, 1914, p. 1153.
1	After operation for cholecystitis.	....	1	.....	Baugher, J. A. M. A., Apr. 11, 1914, p. 1153.
1	After operation for appendicitis.	....	1	.....	Baugher, J. A. M. A., Apr. 11, 1914. p. 1153.
1	Carcinoma of liver.	1	....	3 months before death.	Present communication.

* "Practical Bacteriology, Microbiology and Serum Therapy" (English edition). Longmans.

an infectious process extending probably from the gall-bladder into the liver, whence toxins* and organisms reached the general circulation with the results manifested during life.

It is, of course, possible that antecedent injury of the gall-bladder by the activities of the organism in question furnished that continued irritation thought to be so important in determining the site of a neoplasm.

An interesting feature of this case was the positive blood culture obtained three months before death. In the literature

FIG. 1.—Gall-bladder and gall-stones from case of chronic cholecystitis due to *B. aërogenes capsulatus*.

positive blood culture cases (showing the *B. aërogenes capsulatus*) are so rare as to justify a résumé of those found, which are given in the table opposite.

A somewhat similar case was one recently operated upon by Dr. G. de Yoanna of this city, in which he removed the gall-bladder shown in the accompanying illustration. The patient, Mrs. C., was a married woman, 30 years of age, who had complained of repeated attacks of indigestion. When Dr. de Yoanna examined her abdomen he readily detected the projecting mass formed by the diseased gall-bladder. It was not tender and the patient was afebrile, but, since the finding was so markedly pathological, he determined to operate. The diseased structure, although extensively adherent to adjacent organs, was removed but, unfortunately, the patient died two days later.

Upon examination of the gall-bladder I could find no lesions other than excessive hypertrophy of its muscular and fibrous elements (its wall was over three-quarters of an inch thick) and catarrhal inflammation of the mucosa. The gall-bladder contained, besides the gall-stones shown in the photograph, nearly clear serous fluid in which I found many bacilli, most of which were in the degenerated state connected with spore formation. Cultures from this fluid gave a pure growth of the *B. aërogenes capsulatus*. The gall-stones were of cholesterin, and from the centers of two of them I grew a culture of the same organism, this indicating that it probably was concerned in the formation of the concretions.

IDENTIFICATION OF ORGANISMS

In the case of the blood culture from Mrs. B., the first organisms that were obtained were from the bottom of a narrow tube of about 10 c. c. of bouillon, to which had been added 0.5 c. c. of the patient's blood. These bacilli were observed after 48 hours' incubation, at 37.5° C.* Replants in bouillon, after two to three generations, diffusely clouded the medium. The organisms were non-motile. In old cultures many of the bacilli showed the non-stain-taking oval form associated with spore formation. Cultures (replants from bouillon) in neutral milk, within 24 to 48 hours, coagulated the medium with acid reaction and rancid odor. Replants in dextrose-agar developed bubbles of gas. Young organisms were always gram-positive.

A guinea-pig, intravenously inoculated with 0.5 c. c. of a culture in bouillon-serum, was killed a few minutes later, incubated for 24 hours and autopsied. Gas was found in the heart, the larger veins, and in the liver. Many large capsulated bacilli were evident in smears made from the blood.

In the second case (Mrs. C.) a culture, from the nucleus of a gall-stone, in bouillon-serum, was replanted in milk, which it coagulated, as above, giving an odor of butyric acid.

A bouillon-serum culture (0.5 c. c.) was injected into a guinea-pig, which was killed five minutes later, incubated for 24 hours and autopsied. Bubbles of gas, and capsulated bacilli were found as in the case first described.

RECENT BACTERIOLOGICAL WORK

Work of a great deal of interest has been published during the past year in connection with the conditions affecting the growth of this bacillus. Wright* conducted extensive experiments by which he showed that it would grow most prolifically

* Bull and Pritchett (J. Med., 1917, XXVI, pp. 119) recently demonstrated that this bacillus could produce a toxin which was hæmolytic and able to disintegrate tissue elements generally.

* Besson (p. 570) quotes Rosenthal to the effect that the latter had grown the bacillus under aërobic conditions. Baugher (quoted before) did not employ anaërobic conditions in growing his blood cultures.

in a tube of bouillon to which a piece of potato (or various other substances) had been added, under aërobic conditions. Since he obtained similar results by adding to the bouillon, instead of potato, pledgets of cotton or of asbestos wool, platinum black, a rusty nail, a capillary glass tube filled with a minute quantity of a suspension of the organisms, he concluded that the common factor involved was of a mechanical nature. He says: "And that mechanical factor would appear to be the providing of some hole or cranny to serve as a nidus in which the microbe can get a start by concentrating its chemical effort at first upon a fractional portion of the provided culture medium."

Continuing his experiments he determined that trypsinized serum was considerably more favorable to the growth of the organism than normal serum, and declared that what he calls the "antitryptic power of the blood" stood in the way of the growth of this organism, as well as of others, by inhibiting the digestive processes by which microorganisms obtain their food. Of course, it seems that this so-called antitryptic power may represent nothing more than the minimal power (amount) of bacterial enzyme that is required to make a salient (militarily speaking) into the normal serum or blood elements, or the resistance to bacterial digestion (the chemical inertia) displayed by the smallest units of the said serum upon which the bacterial forces can be brought to bear.

Wright, commenting upon the difficulty met with in starting growth of cultures of the *B. aërogenes capsulatus* in serum and the avalanche-like progress made when once such a start had been effected, compared this to the way in which wound infections with this organism often become rapidly progressive.

Considering the acidity developed in serum by the growth of this bacillus he experimented with serum of which the natural alkalinity had been neutralized by the addition of sulphuric acid, and found that the addition of the acid converted an unfavorable into a most favorable medium. The lesson of this experiment was applied clinically, and Wright reports that the administration of alkalies to patients suffering from serious wound infections with the bacillus in question "gave markedly favorable results only in two cases out of the six" experimented upon.

In this connection it occurs to the writer that the reason the addition of acid, especially a mineral acid, to an albuminous fluid such as blood serum, aids in the growth of a peptonizing microorganism therein, is that here the same forces operate as in the human stomach where peptic digestion is so greatly dependent upon the presence of acid.

Taylor and Austin[10] recently announced that "Dakin's hypochlorite and chloramine-T solutions will protect pigeons against multiple fatal doses of the toxin of *B. welchii* when the antiseptic and the toxin are mixed *in vitro* and allowed to stand in contact for five minutes before injection. The detoxicating action of the solutions is demonstrable also in the presence of serum. Phenol solution, 0.25 per cent, has no such action."

They quote Dakin to the effect that this action of the chlorinated antiseptics is to be attributed chiefly to their affinity for the amino group of the protein molecule. It seems to me that a simpler and more probable explanation would be that thse solutions acted in an antacid capactity upon a toxin which Wright proved to be more active in an acid or at least a neutral medium. The failure of the phenol to modify the effect of the toxins may be explained along the same lines, as it would tend to increase acidity, certainly not to reduce it.

Wolf, McGill and Harris,[11] after experimenting with this same organism along the lines pursued by Wright, announced that "with a properly prepared culture medium *B. welchii* will grow freely in open, narrow tubes. The addition of any solid matter is not necessary to produce this apparently aërobic growth. No segregation of organisms is necessary, for the bacillus grows vigorously when nitrogen containing 1 per cent of oxygen is bubbled continuously through the tubes, but the organism is very sensitive to, and its growth is inhibited by, higher proportions of oxygen. For this reason the so-called aërobic growth is best obtained in narrow tubes of freshly sterilized fluid from which the air has been partly expelled by the heat of sterilization."

In regard to the layer of oil that some have thought necessary and so frequently employ in cultivating certain organisms, a statement by these authors is most interesting and undoubtedly entirely true:

"In connection with the conditions which are usually associated with anaërobic technique it would appear that bacteriologists have been deluded for a long time into thinking that by covering a culture medium with a layer of paraffin or lanoline the aqueous layer is protected from the gases of the atmosphere. Vernon, as quoted by Bayliss in his "Principles of General Physiology," found that oxygen was 4.5 times more soluble in fats and oils than in water. Bayliss directs attention to the futility of attempting to protect aqueous solutions from the gases of the atmosphere with layers of oil, as is done in Hesse's method. The anaërobic conditions desired can be just as well obtained by employing high, narrow tubes of freshly sterilized media.

"We have a certain number of experiments which confirm Bayliss's statement in every particular. Sloped tubes covered with paraffin do not grow the bacillus any better than do similar tubes unprotected by the fatty layer. If the paraffin layer is of any real value, it probably plays its part in diminishing convection currents in the aqueous layer."

REFERENCES

1. Welch and Nuttall: Bull. Johns Hopkins Hospital, 1892, III, 81.
2. Gwyn: Bull. Johns Hopkins Hospital, 1899, X, 134.
3. Libman: Bull. Johns Hopkins Hospital, 1906, XVII, 215.
4. Baugher: J. Am. Med. Ass., 1914, LXII, 1153.
5. Orton: J. Medical Research, 1913, XXIX, 287. Sylvester and Hibben: Arch. Ped., 1915, XXXII, 457. Hewes and Kendal: Boston M. & S. J., 1912, CLXVI, 75.
6. Cone: American J. Orth. Surg., 1914, XI, 389.
7. Shortlidge: California St. J. Med., 1912, X, 160.
8. Cramp: Annals of Surgery, 1912, LXI, 544.
9. Wright: London Lancet, 1917, CXCII, 1.
10. Taylor and Austin: Jour. Exp. Med., 1918, XXVII, 37.
11. Wolf, McGill and Harris: London Lancet, 1917, CXCIII, 787.

ABSTRACT OF PAPER

Representing Work Done in The Johns Hopkins Hospital, but Published or to be Published Elsewhere than in the Bulletin Prepared by the Authors

OBSERVATIONS UPON THE CALCIUM CONTENT OF THE BLOOD IN INFANTILE TETANY AND UPON THE EFFECT OF TREATMENT WITH CALCIUM

By John Howland and W. McKim Marriott

(From the Harriet Lane Home of The Johns Hopkins Hospital and from the Department of Pediatrics of The Johns Hopkins University, Baltimore)

The diagnosis of tetany at the present day from clinical symptoms and by means of the accessory diagnostic signs may be made with sufficient accuracy; it is another matter to determine what it is that brings about this strange hyperexcitability of the nervous system to insults and stimuli of all kinds. There have been many hypotheses suggested. None has been as yet entirely convincing. It has been vigorously insisted that tetany is only a symptom of rickets. It is quite true that rickets is usually to be found associated with tetany and that tetany is most common during the winter and spring months when active rickets is also most frequently seen. The chief objections to this hypothesis are that tetany is found at times when no rickets is discoverable and that very many children with the most extreme evidences of rickets never manifest any evidences of tetany.

Tetany has been referred to an improper diet, to an absence of breast milk or to an excessive quantity of cow's milk. That no particular food can be held solely responsible is shown by the fact that tetany may be seen after almost any form of diet.

Tetany has also been referred to the absence of an essential substance or "vitamine" in the diet. In support of this view may be mentioned the preponderance of tetany among the artificially fed and the considerable improvement brought about by codliver oil. Against this view is the fact that many cases of tetany are to be seen when the diet of the infants has been composed wholly or in part of cow's milk which has not been heated and hence still contains the vitamines.

Noël Paton and his collaborators have recently made an extensive study of tetany in animals and in human beings. They believe that the tetany of animals deprived of their parathyroid glands and the idiopathic tetany of infants are similar as regards their characters and metabolism, and that both are due to some error in metabolism whereby an intoxication by guanidin and methyl guanidin takes place. Until the chemical studies upon which these conclusions are based can be repeated and confirmed, it would be premature to venture a definite opinion regarding them. There are certain facts, however, that merit consideration. In the first place, enough studies have been made to show that parathyroid lesions in infantile tetany are the exception and not the rule. It should also be stated that parathyroid lesions as severe as have been found after tetany may occur in patients who, during life, have shown absolutely no evidences of tetany, electrical or otherwise. Another possible ground for criticism of Paton's conclusions is found in the small number of observations upon children and in the unsatisfactory ages of the children used for control. Finally, granting that the analytical method used by Paton determines guanidin and methyl guanidin alone, no proof has been brought forward that the substances have accumulated in the blood of children.

Some objections to the view that parathyroid disease is the cause of infantile tetany have been mentioned. That there are many points of similarity between the tetany of parathyroidectomized dogs and human tetany is true. The symptoms are much alike as are also the electrical reactions. The changes that MacCallum and Voegtlein found in the calcium of the blood are, as will be seen later, strikingly like those that we have found in the tetany of infants. But the experiments of Binger show that typical tetany may be produced in dogs when the parathyroids are left entirely undisturbed.

More attention has probably been paid to calcium as a factor in the production of infantile tetany than to any other chemical substance. The close connection between rickets and tetany, in the former of which there is a known error of calcium metabolism, has been sufficient to suggest to many a somewhat similar disturbance of calcium metabolism in tetany. A great stimulus to the study of the relation of calcium to tetany was given by the observation of Sabbatani and other Italian investigators, that a solution of calcium applied to the brain diminished its irritability to electrical stimulation, but substances that caused a precipitation of calcium such as oxalates or citrates brought about an increased irritability.

The favorable therapeutic influence of calcium upon tetany gives weight to the view that a deficiency of calcium may play a part in the production of tetany. Studies upon the calcium metabolism of infants with tetany have been made by v. Cybulski and Schabad. The former found a very slight calcium retention during active tetany and a greatly increased retention during convalescence. Schabad's results were similar. He came to the conclusion that there was absolutely no difference to be determined between the metabolism of uncomplicated rickets and of rickets complicated by tetany and stated that the information to be desired could be obtained only by analyses of the blood. He, however, made none.

The attempt has been made by Neurath, Cattaneo, and Longo to determine the calcium in the blood. Neurath used Wright's method, which is supposed to show differences in the amount of free calciumions. It gives relative but not absolute figures. Neurath examined the blood of 15 infants with various manifestations of tetany of more or less severity. He found in general a reduction of the calcium. No determinations were made upon patients with rickets alone.

Cattanee and Longo have made gravimetric determinations of the calcium in the blood of a few normal children and of

a few with tetany. Their results were at variance and Longo concluded that it was impossible to establish any relationship between the amount of calcium in the blood and any manifestation of tetany.

The studies upon parathyroid tetany in animals are of great interest on account of the influence of parathyroidectomy upon the calcium of the blood. MacCallum and Voegtlein and MacCallum and Vogel have shown that after parathyroidectomy tetany appeared when the calcium of the blood was diminished about one-half and that the symptoms of tetany could be promptly, though only temporarily, relieved by the intravenous administration of calcium salts.

A year ago we showed that in the acidosis of nephritis there is a great accumulation of inorganic phosphates in the blood serum, and that when the phosphates are increased there is a reduction of the calcium, sometimes to a very low point. On the basis of these findings Binger has recently published interesting observations upon the effect of the intravenous administration of phosphate solutions to dogs. When sodium phosphate in sufficient quantity and at the right reaction is injected, definite tetany results with a marked decrease in the calcium of the serum. If the solution injected has a hydrogen-ion concentration greater than 10^{-6} no tetany results even though the calcium drop occurs.

We have studied the relationship of calcium and infantile tetany during the last 2½ years. It is apparent that merely from the determination of the intake and excretion of calcium, little can be learned. It is of prime importance to determine the quantity of calcium circulating in the blood. With the usual methods of analysis this has been impossible unless 50 or 100 c. c. were withdrawn, with double the amount if duplicate determinations were made—an impossible procedure with living infants. It was therefore necessary to develop an accurate method that would allow duplicate determinations to be made with a small amount of blood. This we have done. The method is sufficiently exact to determine the calcium in 2 c. c. of serum with an error of not more than 5 per cent.

We determined first the calcium in the serum of normal persons. The amounts found are given in Table I.

TABLE I.—NORMAL

MILLIGRAMS OF CALCIUM PER 100 C. C. OF SERUM

Placental	11.3	15 months	11.0
Placental	11.0	Adult	11.2
Placental	10.8	Adult	11.3
Placental	10.7	Adult	9.2
6 weeks	11.0	Adult	10.0
3 months	10.0	Adult	10.3
3 months	11.0	Adult	11.0
5 months	10.8	Adult	9.8

It will be seen from the table that the quantity of calcium in placental serum and in the serum of normal patients is singularly constant. In almost all instances, no matter what the age, and in all instances with infants it was above 10 mg. and it is seldom more than 11 mg.

On account of the frequent association of rickets with tetany it was necessary to determine if any changes in the calcium of the serum results from rickets alone. We have therefore studied a considerable number of cases of rickets.

TABLE II.—RICKETS

MILLIGRAMS OF CALCIUM PER 100 C. C. OF SERUM

No.	Child	Race	Age	Type of Rickets	Calcium
1	A. T.	Colored	4 months	Active	10.9
2	R. W.	Colored	4 months	Active	9.0
3	C. J.	Colored	4 months	Active	10.5
4	L. D.	Colored	4 months	Active	7.9
5	D. S.	Colored	4 months	Active	9.0
6	G. D.	Colored	4 months	Active	8.0
7	E. F.	Colored	4 months	Active	9.0
8	H. L.	Colored	4 months	Active	8.3
9	E. B.	Colored	4 months	Active	9.3
10	B. S.	Colored	6 months	Mild	10.9
11	M. S.	White	6 months	Mild	10.7
12	C. F.	White	6½ months	Moderate	8.6-9.0
13	M. S.	White	8 months	Mild	10.9
14	T. L.	White	8 months	Moderate	9.0
15	L. W.	White	8 months	Marked	10.5
16	F. F.	White	9 months	Marked	9.0
17	E. V.	White	10 months	Mild	8.0
18	R. Q.	Colored	12 months	Mild	9.8
19	R. Q.	Colored	14 months	Mild	8.8
20	J. M.	White	20 months	Marked	10.0
21	S. J.	Colored	23 months	Very severe	9.3
				Average	9.4

An examination of the figures in Table II shows that in more than a third of the cases the figures fall within the normal limits, and this even when the disease was presumably active (in the fourth and sixth months). In 9 cases there was a slight reduction, so that there were found between 9 and 10 mg. of calcium per 100 c. c. In 5 cases the calcium content was from 7.9 to 8.8 mg. The lowest amount that we have found in apparently uncomplicated rickets was 7.9 mg. We may say, then, that with rickets there is no great reduction in the calcium, that while the calcium may be reduced as much as 2 mg. per 100 c. c. (20 per cent) the considerable majority show a reduction of 1 mg. (10 per cent) or less, and that with cases of apparently active rickets there may be no reduction whatever. The calcium reduction does not seem to be obligative.

In choosing cases of tetany for study we have taken those regarding the diagnosis of which there could be no doubt whatever. All of the children had had or were having convulsions, with all there was a cathodal opening contraction with a current less than 5 milliampères, a number had spasm of the glottis, and with many Trousseau's sign or a marked facial phenomenon, or both, were demonstrated.

Table III gives in tabular form the calcium in the serum, during active symptoms, with the 18 cases of idiopathic tetany which we have studied.

TABLE III.—ACTIVE TETANY

MILLIGRAMS OF CALCIUM PER 100 C. C. OF SERUM

Case 1	6.0	Case 11	6.0
Case 2	5.7	Case 12	6.5
Case 3	5.5	Case 12	6.15
Case 4	5.0	Case 13	6.3
Case 5	5.0		6.5
Case 6	5.8	Case 14	6.8
Case 7	3.5	Case 15	6.0
Case 8	5.0	Case 16	7.3
	6.3	Case 17	5.0
	5.0	Case 18	4.6
	4.5		
Case 9	4.7		
Case 10	5.8	Average	5.6

It will be noticed that the calcium was very greatly reduced in all instances, and with one exception was 7.0 mg. or less per 100 c. c., a reduction, roughly, in the neighborhood of 40 per cent. It will also be noticed that the calcium was, in all instances, less than we have ever found with rickets and so much lower that, with one or two exceptions, there could be no danger of confusing even the highest determinations with the lowest which we obtained in rickets. From the regularity of our findings it appears that convulsions may be expected when the calcium content of the serum becomes less than 7.0 mg. per 100 c. c., or, to put it in another way, when there are convulsions and other symptoms due to tetany, the calcium of the serum is 7.0 mg., or less, per 100 c. c. The amount of calcium in the serum that we found in idiopathic tetany is strikingly close to that which was found by MacCallum and Vogel in the serum of dogs after parathyroidectomy. They determined the calcium in whole blood. Considering the calcium of serum twice that in an equivalent amount of whole blood, their results may be reckoned as 3.1, 6.4, 4.5, and 7.8 mg. per 100 c. c.

The results obtained by Binger are also strikingly similar. He found that dogs, after injection with a sodium phosphate solution of the proper hydrogen-ion concentration, developed tetany when the calcium in the serum was 5.6, 6.1, 5.5, and 5.3 mg., respectively, and that tetany did not develop when the calcium of the serum was reduced by the same measures to 7.8, 7.7 and 7.7. mg., respectively. We have also found in studying the serum of two dogs subjected to parathyroidectomy that the symptoms of tetany developed when the calcium was reduced to about 7.0 mg. Thus, one dog, before operation, had 10.8 mg. of calcium per 100 c. c. of serum; after 48 hours, a short time before the onset of tetany, 7.3 mg., and the second had, before operation, 10.0; after 24 hours, 8.9; and after 6 days and with the onset of tetany, 6.8 mg., per 100 c. c. of serum.

The constancy in the diminution of the calcium of the serum in tetany affords some means of differentiating tetany from other convulsive disorders in infancy. We have studied other cases of convulsions, manifestly not due to tetany, and have found the following:

TABLE IV.—CASES OF CONVULSIONS NOT DUE TO TETANY

Patient	Age	Diagnosis	Mg. of Calcium per 100 c. c. of Serum
S. S.	4 months	Mental deficiency	10.1
C. deF.	1 year	Petit mal	11.0
D. N.	2½ years	Epilepsy	10.2
J. B.	5 years	Epilepsy	8.9
R. G.	7 months	Convulsions of unexplained origin	9.6
M S.	6 months	Convulsions of unexplained origin	10.7
H. B.	7 months	Convulsions of unexplained origin	9.2

In the light of these results is it possible to refer tetany to a diminution of calcium in the blood? Perhaps the strongest evidence, in addition to the great parallelism which we have found between the symptoms and the low calcium content of the serum, is the results obtained by Binger after the injection of orthophosphates. When the calcium was reduced to a figure closely corresponding to what we found with active tetany, the characteristic symptoms of tetany in the dog appeared, and this when the parathyroids were entirely untouched. The prompt improvement in infantile tetany after calcium medication, as will be shown, and the absence of symptoms when the calcium in the blood remains above 7.5 mg., is also strong evidence as to the part that calcium plays in the production and dissipation of symptoms.

It seems sufficiently plain that the diminution in the calcium of the serum is a constant phenomenon in infantile tetany. What is it that brings about this diminution?. The question arises: Is there an accumulation of inorganic phosphates of the serum in tetany sufficient to account for the reduction of the calcium? This question can be answered at once in the negative. We have determined the inorganic phosphorus, in active tetany, the calcium being low, and have not found an amount of phosphorus in the serum significantly above the normal limits, which are from 1 to 3.5 mg. per 100 c. c. of serum. We have found in tetany 1.0, 3.0, 4.0 and 2.7 in different cases.

Wilson, Stearns, and Thurlow showed that in dogs at certain stages of tetany induced by parathyroidectomy, there was an increased alkalinity of the blood called by them "alkalosis." This disappeared after the onset of convulsions. We have made determinations of the hydrogen-ion concentration of the serum of infants with tetany by the dialysis indicator method but have not found an "alkalosis." That tetany may, however, at times result from an alteration in the reaction of the blood we have had opportunity to observe. After the therapeutic administration of bicarbonate of soda for acidosis, it is not unusual to see the development of characteristic symptoms of tetany. Thus, we have seen typical carpopedal spasm when bicarbonate of soda has been injected intravenously for the acidosis of diarrhœa. The onset of symptoms of tetany following the administration of soda and their prompt cessation when the soda was stopped, with the changes in the calcium content of the serum and the electrical reactions, indicate that soda is capable of producing these symptoms.

It is apparent that the symptoms of tetany and the lowering of the calcium content of the serum may be produced in a variety of ways, but we have not been able to show that any of these means is operative in uncomplicated infantile tetany.

Calcium and magnesium, both constituents of the serum, are chemically closely related, and from the physiological standpoint it has been shown that their action is frequently similar though at times it may be distinctly antagonistic. For this reason it appeared advisable to determine also the magnesium in the serum. It was necessary to devise a special method for this as the amount in the serum is so small that gravimetric determinations are out of the question. This we have done. The method is sufficiently accurate to determine the magnesium in 2 c. c. of serum with an error of not more than 5 per cent. The determination may be made with the same sample of serum in which the calcium is determined. It has been found that the amount of magnesium in the serum shows but little variation. Not only is this true during health but it is also true in disease. We have not found less than 1.75 mg. or more than 4.0 mg. of magnesium per 100 c. c. of serum. The slight variations in the magnesium seem to bear no relationship to the alternations in the calcium. It is, therefore, possible to say that magnesium plays no determining rôle in the production of the symptoms of tetany.

Our results are sufficiently numerous to allow certain conclusions to to be drawn regarding the specificity of the electrical recations of tetany. In all instances when the C. O. C. or C. C. T. occurred with a current of less than 5 milliampères, there were unmistakable evidences of tetany and a very distinct reduction in the calcium of the serum. This is another way of demonstrating the specificity of the cathodal hyperexcitability of Thiemich and Mann which, from clinical experience, has been considered satisfactory evidence of the presence of tetany.

The influence of calcium upon the symptoms of tetany has been studied in two ways. Bogen, Risel, Rosenstern, von Pirquet, Zybell and others gave calcium in various forms and in various doses; but they gave usually only one dose and determined the effect of its administration upon the electrical reactions. From the single dose no effect or only a temporary effect, upon the clinical symptoms was observed. Others, notably Netter and Göppert, have consistently used calcium in the treatment of tetany and have reported striking results from its use, when repeated doses have been administered. Its usefulness has not been demonstrated except by the dissipation of clinical symptoms, *i. e.*, its effect upon the electrical reactions or upon the other signs has not been noted. With the proof that in active tetany the calcium in the serum is consistently low, it has been the logical thing to give calcium and to give calcium repeatedly, for if there is a constant calcium loss it is only by the continued administration of calcium that a sufficient quantity to prevent symptoms can be kept circulating in the blood. If the administration of calcium is interrupted it soon sinks again to its previous low level. We have, therefore, given calcium by mouth in doses of from 0.5 gm. to 1.0 gm. every 4 hours. We have also determined the effect of this administration of calcium upon the electrical reactions and upon the calcium content of the serum as well as upon the clincial symptoms. It may be stated without reservation that calcium has a very prompt effect in preventing all of the symptoms of active tetany. In the course of a few hours the symptoms diminish in intensity and almost always in 36 or 48 hours they have entirely disappeared. The electrical reactions also undergo an alteration so that C. C. T. or a C. O. C. with a current of less than 5 milliampères is no longer obtained. The calcium content of the serum also rises. In some instances it has reached nearly normal in the course of a few days. In the majority of instances, however, it has not reached normal, but has remained between 7.5 and 9 mg. for a long time, despite the continued administration of calcium. The symptoms, however, have been held entirely in abeyance. We know of hardly another drug which acts in disease with the promptness and with the regularity that calcium does in tetany. The calcium administration must, however, be continued. The cessation of the drug for a few days, perhaps even hours, will allow the return of symptoms and it is altogether probable that in many instances it must be continued until in the ordinary course of events the tendency to tetany disappears. This is added evidence to us that the calcium deficiency in tetany is not a primary condition. It is brought about by some unknown factor which diminishes to a very marked degree the calcium content of the serum, which is operative chiefly during certain months of the year and which gradually loses its effect or disappears.

We employed calcium lactate at first. It did not appear to us that the effects were so prompt as those produced by calcium chloride. For this reason we have given calcium chloride in the great majority of instances. This has been administered in the food. We have continued the calcium in most instances for several weeks and have then gradually diminished the amount and frequency of administration until it was discontinued entirely.

It is undoubtedly true that in many instances phosphorus and codliver oil have a distinct effect in improving tetany. At times, however, their influence is slight. In any event it is slow and is often not sufficiently marked or sufficiently prompt to prevent the development of dangerous or perhaps fatal symptoms. Whilst, therefore, these substances are indicated they can by no means take the place of calcium. In the presence of severe or dangerous symptoms, chloral, morphine, and chloroform and magnesium sulphate hypodermatically must be used in sufficient amount and frequently enough repeated to hold the symptoms in check until calcium in full doses produces its sedative effect. This is usually within 36 or 48 hours. Thereafter only the calcium need be given. Further investigations will show whether the influence of phosphorus and codliver oil is similar to that of the calcium, and that when its administration is discontinued, the calcium in the serum again sinks to a low level, or whether it has a more fundamental effect than the calcium administration and over-

comes the factors that are responsible for the deficiency of circulating calcium.

Our conception of tetany is that some factor, at present unknown, causes a reduction of the calcium content of the blood. When this reaches an amount roughly between 6.0 and 7.0 mg. of calcium per 100 c. c. of serum, frank evidences of tetany arise. This amount, however, is not the same with all individuals. With some it may be as low as 5.5 or 6.0, with others, as high as 7.5. These symptoms occur in outbursts so long as the calcium remains low. When the calcium rises the symptoms disappear. The height to which the calcium must rise in order that the symptoms must disappear is also somewhat variable. We believe that many of the symptoms are directly referable to the diminished calcium content of the blood and that they may be prevented or caused to disappear by repeated doses of calcium.

BOOKS RECEIVED

Medical Service at the Front. By Lieut.-Col. John McCombe, C. A. M. C., and Capt. A. F. Menzies, M. C., C. A. M. C. Illustrated. 1918. 24°. 128 pages. Lea & Febiger, Philadelphia and New York.

Lessons from the Enemy. How Germany Cares for Her War Disabled. By John R. McDill, M. D., F. A. C. S. Illustrated. Medical War Manual No. 5. 1918. 24°. 262 pages. Lea & Febiger, Philadelphia and New York.

Modern Operative Bone Surgery. With Special Reference to the Treatment of Fractures. By Charles George Geiger, M. D. With 120 illustrations. 1918. 8°. 286 pages. F. A. Davis Company, Publishers, Philadelphia; Stanley Phillips, London.

University of Illinois, College of Medicine, Chicago. Collected Studies from the Department of Pathology and Bacteriology. Volume III, 1917. 8°. Chicago, Ill.

The Technique of Psychoanalysis. By Smith Ely Jelliffe, M. D. Nervous and Mental Disease Monograph Series No. 26. 1918. 8°. 163 pages. Nervous and Mental Disease Publishing Company, New York and Washington, D. C.

The General Education Board. Report of the Secretary 1916-1917. 8°. 92 pages. The General Education Board, New York City.

A List of Books by Some of the Old Masters of Medicine and Surgery. Together with Books on the History of Medicine, and on Medical Biography, in the Possession of Lewis Stephen Pilcher; with Biographical and Bibliographical Notes, and Reproductions of Some Title Pages and Captions. 1918. 8°. 201 pages. Brooklyn, N. Y.

American Gynecological Society. Album of the Fellows, 1876-1917. LeRoy Broun, B. S., M. D., F. A. C. S., Editor. 1918. 8°. 532 pages. William J. Dornan, Printer, Philadelphia.

Applied Bacteriology. Studies and Reviews of Some Present-Day Problems, for the Laboratory Worker, the Clinician, and the Administrator. Edited by C. H. Browning, M. D., D. P. H. Contributors: C. H. Browning, W. Gilmour, R. Gulbransen, T. J. Mackie, S. Russ, L. H. D. Thornton. 1918. 12°. 291 pages. Henry Frowde; Hodder & Stoughton; Oxford University Press, London.

The Diagnosis and Treatment of Venereal Diseases in General Practice. By L. W. Harrison, D. S. O. 1918. 8°. 482 pages. Henry Frowde; Hodder & Stoughton: Oxford University Press, London.

Collected Papers of the Mayo Clinic, Rochester, Minnesota. Edited by Mrs. M. H. Mellish. Volume IX, 1917. 1918. 8°. 866 pages. W. B. Saunders Company, Philadelphia and London.

Diseases of the Heart. Their Diagnosis, Prognosis, and Treatment by Modern Methods, with a Chapter on the Electro-Cardiograph. By Frederick W. Price, M. D., F. R. C. S. 1918. 8°. 472 pages. Henry Frowde; Hodder & Stoughton, Oxford University Press, London.

The Medical Clinics of North America. Volume I, Number 5, March, 1918. Chicago Number. Published Bi-Monthly. 1918. 8°. W. B. Saunders Company, Philadelphia and London.

Oral Sepsis in its Relationship to Systemic Disease. By William W. Duke, M. D., Ph. B. With 170 illustrations. 1918. 8°. 124 pages. C. V. Mosby Company, St. Louis.

Reclaiming the Maimed. A Handbook of Physical Therapy. By R. Tait McKenzie, M. D. Illustrated. 1918. 24°. 128 pages. Macmillan Company, New York.

Infection and Resistance. An Exposition of the Biological Phenomena Underlying the Occurrence of Infection and the Recovery of the Animal Body from Infectious Disease. By Hans Zinsser, M. D. With a Chapter on Colloids and Colloidal Reactions. By Professor Stewart W. Young. Second edition revised. 1918. 8°. 585 pages. Macmillan Company, New York.

The Prevention of Venereal Diseases. By Otto May, M. A., M. D. (Cantab.), M. R. C. P. (London), 1918. 12°. 240 pages. Henry Frowde; Hodder & Stoughton; Oxford University Press, London.

The Medical Report of the Rice Expedition to Brazil. By W. T. Councilman, M. D., and R. A. Lambert, M. D. 1918. 8°. 126 pages. Harvard University Press, Cambridge.

Chemistry of Food and Nutrition. By Henry C. Sherman, Ph. D. Second edition, rewritten and enlarged. 1918. 8°. 454 pages. The Macmillan Company, New York.

Surgery of the Spine and Spinal Cord. By Charles H. Frazier, M. D., Sc. D., with the Collaboration of Alfred Reginald Allen, M. D. With six colored plates, two charts and three hundred and seventy-five illustrations in the text. 1918. 8°. 971 pages. D. Appleton and Company, New York and London.

Cornell University Medical Bulletin. Volume VII, Number 4, April, 1918. Studies from the Department of Psychiatry. 1918. 8°. Published by Cornell University, New York City.

Connecticut State Medical Society. Proceedings 1918. 126th Annual Convention. Editor, John E. Lane. 1918. 8°. 266 pages. Published by the Society, New Haven, Connecticut.

The Treatment of War Wounds. By W. W. Keen, M. D., LL. D. Second edition, reset. 1918. 12°. 276 pages. W. B. Saunders Company, Philadelphia and London.

A Diabetic Manual for the Mutual Use of Doctor and Patient. By Elliott P. Joslin, M. D., Illustrated. 1918. 12°. 187 pages. Lea & Febiger, Philadelphia and New York.

Bulletin of Iowa Institutions (Under the Board of Control). Published quarterly. Volume XIX. 1917. 8°. 323 pages. Des Moines, Iowa.

Rockefeller Institute for Medical Research, N. Y. Studies. Reprints. Volume XXVIII. 1918. 8° 661 pages. The Rockefeller Institute for Medical Research, New York.

THE JOHNS HOPKINS HOSPITAL REPORTS.

VOLUME I. 423 pages, 99 plates.

VOLUME II. 570 pages, with 28 plates and figures.

VOLUME III. 766 pages, with 69 plates and figures.

VOLUME IV. 504 pages, 33 charts and illustrations.

VOLUME V. 480 pages, with 32 charts and illustrations.

The Malarial Fevers of Baltimore. By W. S. THAYER, M. D., and J. HEWETSON, M. D.
A Study of some Fatal Cases of Malaria. By LEWELLYS F. BARKER, M. B.

Studies in Typhoid Fever.

By WILLIAM OSLER, M. D., with additional papers by G. BLUMER, M. D., SIMON FLEXNER, M. D., WALTER REED, M. D., and H. C. PARSONS, M. D.

VOLUME VI. 414 pages, with 79 plates and figures.

VOLUME VII. 537 pages with illustrations.

VOLUME VIII. 552 pages with illustrations.

VOLUME IX. 1060 pages, 66 plates and 210 other illustrations.

Contributions to the Science of Medicine.

Dedicated by his Pupils to WILLIAM HENRY WELCH, on the twenty-fifth anniversary of his Doctorate. This volume contains 38 separate papers.

VOLUME X. 516 pages, 12 plates and 25 charts.

Structure of the Malarial Parasites. Plate I. By JESSE W. LAZEAR, M. D.
The Bacteriology of Cystitis, Pyelitis, and Pyelonephritis in Women, with a Consideration of the Accessory Etiological Factors in these Conditions, and of the Various Chemical and Microscopical Questions involved. By THOMAS R. BROWN, M. D.
Cases of Infection with Strongyloides Intestinalis. (First Reported Occurrence in North America.) Plates II and III. By RICHARD P. STRONG, M. D.
On the Pathological Changes in Hodgkin's Disease, with Especial Reference to its Relation to Tuberculosis. Plates IV-VII. By DOROTHY M. REED, M. D.
Diabetes Insipidus, with a Report of Five Cases. By THOMAS B. FUTCHER, M. B. (Tor.).
Observations on the Origin and Occurrence of Cells with Eosinophile Granulations in Normal and Pathological Tissues. Plate VIII. By W. T. HOWARD, M. D., and R. G. PERKINS, M. D.
Placental Transmissions, with Report of a Case during Typhoid Fever. By FRANK W. LYNCH, M. D.
Metabolism in Albuminuria. By CHAS. P. EMERSON, A. B., M. D.
Regenerative Changes in the Liver after Acute Yellow Atrophy. Plates IX-XII. By W. G. MACCALLUM, M. D.
Surgical Features of Typhoid Fever. By THOS. MCCRAE, M. B., M. R. C. P. (Lond.), and JAMES F. MITCHELL, M. D.
The Symptoms, Diagnosis, and Surgical Treatment of Ureteral Calculus. By BENJAMIN R. SCHENCK, M. D.

VOLUME XI. 555 pages, with 38 charts and illustrations.

Pneumothorax: A historical, clinical, and experimental study. By CHARLES P. EMERSON, M. D.
Clinical Observations on Blood Pressure. By HENRY W. COOK, M. D., and JOHN B. BRIGGS, M. D.
The value of Tuberculin in Surgical Diagnosis. By MARTIN B. TINKER, M. D.

VOLUME XII. 548 pages, 12 plates and other illustrations.

The Connective Tissue of the Salivary Glands and Pancreas with its Development in the Glandula Submaxillaris. Plates I-III. By JOSEPH MARSHALL FLINT, M. D.
A New Instrument for Determining the Minimum and Maximum Blood-Pressures in Man. Plates IV-X. By JOSEPH ERLANGER, M. D.
Metabolism in Pregnancy, Labor, and the Puerperium. By J. MORRIS SLEMONS, M. D.
An Experimental Study of Blood-Pressure and of Pulse-Pressure in Man. Plates XI and XII. By JOSEPH ERLANGER, M. D., and DONALD R. HOOKER, A. B., M. S.
Typhoid Meningitis. By RUFUS I. COLE, M. D.
The Pathological Anatomy of Meningitis due to Bacillus Typhosus. By WILLIAM G. MACCALLUM, M. D.
A Comparative Study of White and Negro Pelves, with a Consideration of the Size of the Child and Its Relation to Presentation and Character of Labor in the Two Races. By THEODORE F. RIGGS, M. D.
Renal Tuberculosis. By GEORGE WALKER, M. D.

VOLUME XIII. 605 pages, with 6 plates, 201 figures, and 1 colored chart.

Studies in Genito-Urinary Surgery.

The Seven-Glass Test. By HUGH H. YOUNG, M. D.
The Possibility of Avoiding Confusion by Bacillus smegmatis (Smegma bacillus) in the Diagnosis of Urinary and Genital Tuberculosis. An Experimental Study. By HUGH H. YOUNG, M. D., and JOHN W. CHURCHMAN, M. D.
Urethral Diverticula in the Male. By STEPHEN H. WATTS, M. D.
An Unusual Case of Urethrorrhagia. By H. A. FOWLER, M. D.
Paraurethritis. By JOHN W. CHURCHMAN, M. D.
Use of Ointments in the Urethra in the Treatment of Chronic Urethritis. By HUGH H. YOUNG, M. D.
Treatment of Stricture of the Urethra. By HUGH H. YOUNG, M. D., and JOHN T. GERAGHTY, M. D.
The Treatment of Impermeable Stricture of the Urethra. By HUGH H. YOUNG, M. D.
The Treatment of Bacteriuria by Internal Medication. By JOHN W. CHURCHMAN, M. D.
Use of the Cystoscope in the Diagnosis of Diseases of the Prostate. By HUGH H. YOUNG, M. D.
Chronic Prostatitis. An Analysis of 358 Cases. By HUGH H. YOUNG, M. D., JOHN T. GERAGHTY, M. D., and A. R. STEVENS, M. D.
Modern Method for the Performance of Perineal Lithotomy. By HUGH H. YOUNG, M. D.
Operative Treatment of Vesical Diverticula. By HUGH H. YOUNG, M. D.
Case of Double Renal Pelvis and Bifid Ureter. By HUGH H. YOUNG, M. D.
Pyonephrosis Due to Bacillus Typhosus. By HUGH H. YOUNG, M. D., and LOUIS C. LEHR, M. D.
The Use of the X-ray in the Diagnosis of Renal and Ureteral Calculi. By F. H. BAETJER, M. D.
Nephritis and Hæmaturia. By H. A. FOWLER, M. D.
The Microscopic Structure of Urinary Calculi of Oxalate of Lime. By H. A. FOWLER, M. D.
Cystinuria with Formation of Calculi. By H. A. FOWLER, M. D.
Post-Traumatic Atrophy of the Testicle. By JOHN W. CHURCHMAN, M. D.
A Description of the Dispensary for Treatment of Genito-Urinary Surgical Cases at The Johns Hopkins Hospital. By HUGH H. YOUNG, M. D.

VOLUME XIV. 632 pages, with 97 figures.

Studies in Genito-Urinary Surgery.

The Treatment of Prostatic Hypertrophy by Conservative Perineal Prostatectomy. An analysis of cases and results based on a detailed report of 145 cases. By HUGH H. YOUNG, M. D.
Recto-Urethral Fistulæ. Description of New Procedures for their Prevention and Cure. By HUGH H. YOUNG, M. D.
The Early Diagnosis and Radical Cure of Carcinoma of the Prostate, being a study of 40 cases and presentation of a radical operation which was carried out in four cases. By HUGH H. YOUNG, M. D.

VOLUME XV. 542 pages, with 87 illustrations.

Twelve papers on pneumonia. By DRS. CHATARD, FABYAN, EMERSON, MARSHALL, MCCRAE, STEINER, HOWARD and HAINES.
A Study of Diarrhœa in Children. By J. H. MASON KNOX, JR., M. D., and EDWIN H. SCHORER, M. D.
Skin Transplantation. By JOHN STAIGE DAVIS, M. D.
Epidemic Cerebrospinal Meningitis and Serum Therapy at The Johns Hopkins Hospital. By FRANK J. SLADEN, M. D.

VOLUME XVI. 670 pages with 151 figures.

Studies in the Experimental Production of Tuberculosis in the Genito-Urinary Organs. By GEORGE WALKER, M. D.
The Effect on Breeding of the Removal of the Prostate Gland or of the Vesiculæ Seminales, or of Both; together with Observations on the Condition of the Testes after such Operations on White Rats. By GEORGE WALKER, M. D.
Scalping Accidents. By JOHN STAIGE DAVIS, M. D.
Obstruction of the Inferior Vena Cava with a Report of Eighteen Cases. By J. HALL PLEASANTS, M. D.
Physiological and Pharmacological Studies on Cardiac Tonicity in Mammals. By PERCIVAL DOUGLAS CAMERON, M. D.

The set of sixteen volumes will be sold, bound in cloth, for ninety dollars, net. Volume II will not be sold separately. Volumes I, III, IV, V, VI, VII, VIII, X, XI, XII, XIII, XIV, XV, XVI will be sold for $5.00, net, bound in paper, and $5.50, net, bound in cloth. Volume IX will be sold for ten dollars, net.

Orders should be addressed to THE JOHNS HOPKINS PRESS, Baltimore, Md.

The Johns Hopkins Hospital Bulletins are issued monthly. They are printed by the LORD BALTIMORE PRESS, Baltimore. Subscriptions, $3.00 a year (foreign postage, 50 cents), may be addressed to the publishers, THE JOHNS HOPKINS PRESS, BALTIMORE; single copies will be sent by mail for fifty cents each. Single copies may also be procured from the BALTIMORE NEWS CO., Baltimore.